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Request for grant of a patent

1/77

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1.	Your reference	TSJ/SVH/42215GB1
2.	Patent application number	0321611.6 15 SEP 2003
3.	Full name, address and post code of the or each applicant	Vectura Ltd 1 Prospect West Wiltshire Chippenham SN14 6FH
	Patents ADP number	8610727001
	If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4.	Title of the invention	Pharmaceutical Compositions
5.	Name of your agent	VENNER, SHIPLEY & CO
	"Address for service" in the United Kingdom to which all correspondence should be sent	20 LITTLE BRITAIN LONDON EC1A 7DH
	Patents ADP	1669004 ✓

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and the or each application number	Country	Priority application number	Date of filing

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and filing date of the earlier application	Number of earlier application	Date of Filing

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'YES' if:*
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Description	52
Claim(s)	4 DL
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Any other documents	

11. I/We request the grant of a patent on the basis of this application.

Signature: Venner, Shipley LLP

Date: 15 September 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Timothy J S Jump
020 7600 4212

DUPLICATE

Pharmaceutical Compositions

The present invention relates to improvements in pharmaceutical compositions comprising the pharmaceutically active agent heparin, for administration by pulmonary inhalation. In particular, the invention relates to dry powder compositions comprising heparin for pulmonary inhalation.

Heparin is a linear polysaccharide which, along with related proteoglycans such as heparan sulphate, is a member of the group of macromolecules referred to as glycosaminoglycans. Owing to their linear anionic polyelectrolyte structure, these macromolecules are involved in various biological processes. While heparin has been used largely for its anticoagulant effects based on its binding to plasma anti-thrombin III, there is evidence that heparin also possesses various anti-inflammatory and immunoregulatory properties, including the modulation of T-lymphocytes, complement activation, inhibition of neutrophil chemotaxis, smooth muscle growth and reduction of intrinsic DNA viscosity.

Heparin is a heterogeneous mixture of variably sulphated polysaccharide chains with a molecular weight range of 6000 to 30000 Daltons. Whole or unfractionated heparin (UFH) may be fractionated to give low and high molecular weight fractions, as is well known in the art. Fractionated, low molecular weight heparin (LMWH) has been shown to reduce the viscoelasticity of dog mucus and improve mucociliary clearance on a frog palate model.

Heparin has been used to treat pulmonary and other diseases. In particular, heparin is used as a mucolytic agent, destroying or dissolving mucin, the chief constituent of mucus. When used as a mucolytic agent, the heparin is preferably administered locally to the respiratory tract, where it can work on the mucus directly.

The mucolytic activity of heparin makes it useful in the treatment of diseases where excess mucus is present in the respiratory tract. Such excess mucus can be present for two reasons. Firstly, there may be hypersecretion of mucus in the airways, which may cause progressive airway obstruction. Secondly, the mucus may have

abnormal viscoelasticity, making it more difficult to clear by mucociliary action or coughing. Both hypersecretion of mucus and abnormal viscoelasticity lead to reduced mucus clearance and increased levels of mucus in the respiratory tract, as seen in a number of pulmonary diseases, including chronic bronchitis, acute asthma, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and bronchiectasis.

Retention of the mucus in the respiratory tract presents a particular problem as it not only obstructs the airways but also facilitates infection and promotes a self-perpetuating cycle of infection and inflammation. Pathological agents such as bacteria (e.g. Pseudomonas aeruginosa) are often able to establish colonies within the mucus. Mucus is a critical component of the primary defence mechanism of the respiratory tract, trapping inhaled particulate and microbial material for removal via the mucociliary system. However, when this mechanism fails to clear sufficiently, mucus accumulates and must be coughed up as sputum, otherwise it is retained in the respiratory tract and can encourage the colonisation by microorganisms which may lead to chronic lung inflammation and obstruction.

Problems arise when the initial bacterial infection stimulates neutrophil chemotaxis, but the neutrophils are unable to effectively clear. Defective neutrophil apoptosis and impaired phagocytosis are key factors in the pathogenesis of lung disease in CF. Neutrophil proteases and oxidants are released during the process and these have a number of effects. They cause both cellular damage and impairment of ciliary movement. They are also potent secretagogues and actually enhance further mucus secretion. The proteases also cleave anti-proteases and cell surface markers, further impairing the host defence mechanisms. Thus, the cycle is perpetuated as these effects further impair mucus clearance at the same time as increasing mucus secretion, encouraging bacterial stasis and promoting airway inflammation. Therefore, the failure of the neutrophils to clear the original infection actually leads to a rapid deterioration of the situation and the process accounts for much of the morbidity and mortality observed in patients with CF.

Classical courses of action taken to treat individuals afflicted with airway hypersecretion and/or abnormal mucus viscoelasticity include antibiotic therapy, administration of bronchiodilators, use of systemic or inhaled corticosteroids, or oral administration of expectorants for liquefaction of the mucus. It is also known to treat the sufferers with aerosol delivered "mucolytic" agents, such as water and hypertonic saline solution. Recombinant human Dnase I (rhDNase) has been used to treat CF sufferers. The rhDNase is thought to enzymatically digest the naked DNA released into the airway surface fluid from bacteria, neutrophils, and other cellular debris. It is this DNA which is supposed to contribute to the elevated viscoelasticity of the mucus in CF sufferers.

The limitations of the currently available treatments are that they appear to be effective in less than 50% of patients. Furthermore, rhDNase is very expensive and hypertonic saline is poorly tolerated in the long term as it causes intense nausea during administration.

Mucin is the principle polymeric component of the mucus gel and consists of a peptide backbone with glycosylated and non-glycosylated domains and oligosaccharide chains. The presence of sulphated and sialic terminals makes the molecule highly polyanionic. The mucins form a polydisperse group of densely charged linear polymers, some of which are up to 6μm in length, with random tangles. The rheological properties are mainly dependent on the tangle density, which in turn is determined by the degree of mucus hydration and mucin molecule length. The necrotic activated neutrophils release large amounts of DNA, actin and proteins which also polymerise and interact with mucin. This process considerably increases the tangle density to form highly viscoelastic mucus gels.

Heparin has been shown to reduce the intrinsic viscosity of DNA. It is thought that heparin may disrupt the interaction between mucin molecules and DNA that occurs in CF sputum, thereby reducing the viscoelasticity of these airway secretions.

The effects of inhalation of an aqueous solution of heparin using a nebuliser on bronchial asthma have been the subject of several studies (nebulisers are

instruments which aerosolise liquid medicament formulations). However, the results of these studies have been inconsistent, possibly because of the difficulty in quantifying the dosages of inhaled heparin reaching the lower respiratory tract.

Pulmonary administration of heparin has been achieved in several studies using dilutions of commercially available solutions of unfractionated heparin (UFH) sodium derived from porcine intestinal mucosa in 0.9% saline, low galactosamine (<2%) (Leo Pharmaceutical Products BV, Netherlands). Various combinations of aqueous heparin formulations and concentrations have been used in a variety of ultrasonic and jet nebulisers. The ultrasonic nebulisers produce aerosols with too great a particle size to reach the deep lung effectively. Although the particle size produced by the jet nebuliser is smaller than that with an ultrasonic nebuliser, just about 3-5μm, it is difficult to estimate the amount of heparin delivered to the lungs from a jet nebuliser due to the evaporative water loss during nebulisation, leading to smaller amounts of drug being deposited in the deep lung than expected.

Tests that have studied the amount of heparin delivered to the deep lung from a nebuliser show that less than 10% of the dose provided reaches its site of action (Bendstrup et al, Eur. Resp. J. 2002; 19; 606-610). It was found that, in order to deliver a deep lung dose of 32,000 IU heparin, a Sidestream jet nebuliser driven at a flow rate of 10 litres a minute required a nebuliser charge of 400,000 IU heparin.

A further problem associated with the use of nebulised heparin is poor patient compliance. Nebulisers are large and cumbersome instruments and treatment requires the patient to be connected to the nebuliser over an extended period of at least half an hour. As only relatively low doses of drug reach the lower respiratory tract via inhalation therapy using a nebuliser, several doses are required, resulting in prolonged therapy resulting in a poor standard of living for the patient being treated.

Heparin is also known for use as an anticoagulant, preventing or retarding the clotting of blood. This effect makes heparin useful in preventing deep vein thrombosis (DVT). Clearly, this therapeutic use of heparin requires the active agent

to be administered systemically, so that it can have an effect on the circulating blood of the patient.

Earlier studies using aqueous heparin showed that a lower respiratory tract dose of 32,000 IU aqueous UFH administered by a jet nebuliser gave no effect on coagulation of circulating blood at clinical level. Accordingly, for the purpose of the discussion of the present invention, a sub-anticoagulant dose of heparin is considered to be less than 32,000 IU reaching the deep lung or lower respiratory tract.

Inhalers are well known devices for administering pharmaceutical products to the respiratory tract by inhalation. Inhalers are widely used, particularly in the treatment of diseases of the respiratory tract.

The lung provides an obvious a target for local administration of formulations which are intended to cure or alleviate respiratory or pulmonary diseases, such as CF, asthma, lung cancer, etc. The lung also provides a route for delivery of systemically acting formulations to the bloodstream.

It is well established that delivering pharmaceutically active agents to the lung by inhalation of a dry powder for inhalation has a number of advantages which make this an attractive mode of delivery. However, the delivery of dry powder formulations of heparin has not previously been contemplated for the treatment of pulmonary diseases. Rather, previously dilutions of heparin solutions have been used. However, these solutions could not be accurately and reproducibly deliver a given dose of heparin to the lower respiratory tract or deep lung, as discussed above.

There has been a reluctance in the past to use heparin in the form of a dry powder for pulmonary inhalation for a number of reasons.

Firstly, it was not previously appreciated that pulmonary inhalation of a dry powder heparin formulation would offer any significant advantage over the nebulised

solutions used. As discussed below, dry powder formulations have also suffered from poor (and unpredictable) levels of administration in the past and so a dry powder formulation would not necessarily be considered to offer any improvement.

Secondly, heparin is known to be a "sticky" compound and this has led to problems formulating it. It is know, as discussed below in greater detail, that dry powder formulations for inhalation suffer from poor efficacy where the fine particles in the formulation agglomerate. Clearly, the sticky nature of heparin is likely to exacerbate the agglomeration, making it very difficult to prepare a dry powder formulation which will efficiently and reproducibly deliver heparin to the lungs.

Indeed, the perceived inability to accurately control the dose administered to the patient using a dry powder formulation presents two problems. If only a low dose of the heparin is administered to the lung, the patient will enjoy little or no reduction in the mucus. However, if the dosing is effective and an unusually high proportion of the heparin is administered to the lung, this could lead to an undesired anti-coagulant effect.

Thirdly, there was a further prejudice against treating the excess mucus in the lungs of a patient suffering from CF, COPD or the like with a powder formulation. Such conditions had, in the past, generally been treated with solutions.

In light of the foregoing, it is an aim of the present invention to improve on the heparin solutions used in the prior art. Furthermore, it is an aim of the invention to provide dry powder compositions comprising heparin for pulmonary inhalation, the compositions being suitable for treating or preventing a range of different diseases, including those which have as a symptom the excess formation of mucus secretions in the airways. The compositions should be suitable for local or systemic administration by pulmonary inhalation, which is a simple and convenient mode of administration which can enhance patient compliance. Significantly, the compositions should provide a predictable, accurate and reproducible dose to that part of the respiratory tract where administration is required to give the desired therapeutic effect. In the case of local treatment of the above discussed pulmonary

diseases, the site of administration is the lungs in general, whereas if systemic administration is required, for example to treat deep vein thrombosis, the heparin must reach much deeper into the lung and will preferably penetrate the alveoli.

The compositions of the present invention are well suited to the treatment of pulmonary and other diseases, whilst overcoming the problems associated with current treatments of such diseases. Preferably, the compositions would be used for treating diseases which have as a symptom the excess formation of mucus secretions in the airways, including chronic bronchitis, acute asthma, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), bronchiectasis, hypersecretion resulting from epithelial damage such as allergic stimuli or mechanical abrasions, and nasal hypersecretion.

Thus, it is a further aim of the present invention to provide a heparin composition for use in treating pulmonary disorders associated with poor mucus clearance, wherein the treatment comprises inhalation of particles of heparin at a dose such that any heparin which enters the patient's bloodstream is at sub-anticoagulant levels, as defined herein.

The compositions of the present invention may also be used to treat diseases or conditions requiring systemic administration of heparin, such as DVT.

Therefore, it is yet another aim of the present invention to provide a composition which comprises heparin and which can be administered at anticoagulant levels for the prophylaxis of deep vein thrombosis. The treatment comprises inhalation of particles of heparin at anticoagulant levels (i.e. at a dose of at least 32,000 IU heparin reaching the deep lung or lower respiratory tract).

The present invention is described below in detail, with reference to the following drawings.

Figure 1 shows a schematic diagram of an ultrasonic nebuliser producing fine droplets.

Figure 2 shows a schematic set-up of a spray drier incorporating an ultrasonic nebuliser.

Figure 3 shows a schematic set-up of a 2-fluid nozzle spray drier.

Figure 4 shows a typical size distribution curve of three repeated tests of pure heparin powder generated using an ultrasonic nebuliser.

Figure 5 shows a comparison between particle size distribution curves of secondary dried and not secondary dried powders. The powder used was heparin and 10% leucine w/w.

Figure 6 shows three repeated size distribution curve of heparin and 5% leucine w/w powder generated by the 2-fluid nozzle spray drier.

Figures 7a-7d are SEM micrographs of 2-fluid nozzle spray dried powders with an increasing percentage of l-leucine (0%, 5%, 25% and 50%), without secondary drying.

Figures 7e-h are SEM micrographs of 2-fluid nozzle spray dried powders with an increasing percentage of l-leucine (2%, 5%, 10% and 50%), after secondary drying.

Figures 8a and b are SEM micrographs of USN spray dried heparin alone and with 10% leucine, without secondary drying.

Figures 9a-c show a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin and leucine at 2% w/w, 5% w/w and 10% w/w.

According to a first aspect of the present invention, a pharmaceutical composition comprising heparin is provided, wherein the composition is a dry powder for administration by pulmonary inhalation.

The composition according to the present invention may be dispensed using any device which is suitable for pulmonary administration of a dry powder. Preferably, the composition is suitable for administration using a dry powder inhaler (DPI).

The heparin used is preferably a heterogeneous mixture of variably sulphated polysaccharide chains with a molecular weight range of 6000 to 30,000 Daltons. Whole or unfractionated heparin (UFH) may be fractionated to give low and high molecular weight fractions, as is well known in the art.

In a preferred embodiment of the present invention, the heparin used in the compositions comprises whole UFH. Prior art studies have shown that low molecular weight fractions of heparin are more effective than whole heparin. However, surprisingly, the inventors have discovered that high molecular weight fractions of heparin are more effective than low molecular weight fractions in reducing human mucus viscoelasticity *in vitro*. Accordingly, in a preferred embodiment of the present invention, the heparin composition comprises a high molecular weight fraction of heparin.

Further, analogues of heparin are commercially available. Such analogues include sulphated heparin and glycosylated heparin. Surprisingly, the inventors have found that sulphated heparin is more effective that non-sulphated heparin in reducing the elasticity of human mucus. Accordingly, in a preferred embodiment of the present invention, the composition comprises sulphated heparin.

The heparin compositions of the present invention may include more than one type or form of heparin. References throughout the specification to heparin are intended to include any of the types or derivatives of heparin known in the art, and mixtures thereof.

The compositions of the present invention may also include other substances, such as stabilisers or excipient materials. The heparin particles will usually comprise at least 1% heparin, and preferably comprise at least 50%, more preferably at least

90% heparin and most preferably at least 95% heparin, and may also include other substances such as stabilisers or excipient materials.

Other particles included in the composition are intended to assist the efficient and reproducible delivery of the active particles from the delivery device to the lower respiratory tract or deep lung and these will be discussed in detail below.

The delivery of dry powder pharmaceutical compositions to the respiratory tract is known to present certain problems. The inhaler device (usually a DPI) should deliver the maximum possible proportion of the active particles expelled to the lungs, including a significant proportion to the lower lung, preferably at the low inhalation capabilities to which some patients, especially asthmatics, are limited. However, when using many dry powder formulations, it has been found that frequently only a small amount (often only about 10%) of the active particles that leave the device on inhalation are deposited in the lower lung. As a result, much work has been done on improving dry powder formulations to increase the proportion of the active particles which is delivered to the lower respiratory tract or deep lung.

The type of dry powder inhaler used will affect the efficiency of delivery of the active particles to the respiratory tract. Also, the physical properties of the powder affect both the efficiency and reproducibility of delivery of the active particles and the site of deposition in the respiratory tract.

On exit from the inhaler device, the active particles should form a physically and chemically stable aerocolloid which remains in suspension until it reaches a conducting bronchiole or smaller branching of the pulmonary tree or other absorption site, preferably in the lower lung. Once at the absorption site, the active particle should be capable of efficient collection by the pulmonary mucosa with no active particles being exhaled from the absorption site.

When delivering a formulation to the lung for local or systemic action, the size of the active particles within the formulation is very important in determining the site of the absorption in the body.

For formulations to reach the deep lung or the bloodstream via inhalation, the active agent in the formulation must be in the form of particles (active particles) that are very fine, for example having a mass median aerodynamic diameter (MMAD) of less than 10μm. It is well established that particles having an MMAD of greater than 10μm are likely to impact on the walls of the throat and generally do not reach the lung. Particles having an MMAD of 5 to 2μm will generally be deposited in the respiratory bronchioles whereas particles having an MMAD of 3 to 0.05μm are likely to be deposited in the alveoli or be absorbed into the bloodstream.

As discussed above, the desired site of administration of the composition of the invention depends upon the condition to be treated by the heparin. Thus, if the heparin is to be administered in order to treat pulmonary diseases such as CF and COPD, the heparin particles preferably have an MMAD of 2-5μm. However, if the composition is to be administered systemically, for example to treat DVT, the heparin particles preferably have an MMAD of less than 5, 3, 2, 1.5 or most preferably 1μm. Preferably, at least 90% by weight of the heparin particles have a diameter within these various preferred ranges.

Due to its polyanionic nature, heparin is a "sticky" molecule and it readily forms aggregates when provided in particulate formation. Such aggregates are too large to reach the deep lung. The inventors have, however, been able to provide particulate heparin formulations which are capable of providing active particles of heparin powder that are capable of being aerosolised in a dry powder inhaler and delivered to the deep lung, and optionally to the bloodstream.

Advantageously, the compositions of the present invention comprise at least 30%, preferably at least 50% and more preferably at least 70% by weight of heparin based on the total weight of the formulation.

However, in addition to the "sticky" nature of heparin, the fine particles are also thermodynamically unstable due to their high surface area to volume ratio, which provides a significant excess surface free energy and encourages particles to agglomerate. In the inhaler, agglomeration of small particles and adherence of such particles to the walls of the inhaler are problems that result in the fine particles leaving the inhaler as large, stable agglomerates, or being unable to leave the inhaler and remaining adhered to the interior of the inhaler or even clogging or blocking the inhaler.

The uncertainty as to the extent of formation of stable agglomerates of the particles between each actuation of the inhaler and also between different inhalers and different batches of particles, leads to poor dose reproducibility. Furthermore, the formation of agglomerates means that the MMAD of the active particles can be vastly increased, so that the agglomerates of the active particles do not reach the desired part of the lung for the required therapeutic effect.

Relatively low doses of heparin are expected to be associated with the benefit of reduced side effects. Administration of low doses of heparin is feasible because the present invention makes it possible to accurately and reproducibly administer a high proportion of heparin in a dose to the appropriate part of the patient's lungs, so that more heparin is administered and more of the administered heparin reaches the target site in the lungs and so can have the desired therapeutic effect.

In particular, the compositions of the present invention firstly provide a high fine particle fraction (FPF) and fine particle dose (FPD) upon aerosolisation of the formulation. Secondly, the compositions comprise particles of the correct MMAD to be deposited in the correct part of the lung. Advantageously, the present invention has identified a number of simple methods of preparing these compositions having good FPFs and FPDs and accurate particle size range.

The metered dose (MD) of a dry powder formulation is the total mass of active agent present in the metered form presented by the inhaler device in question. For

example, the MD might be the mass of active agent present in a capsule for a Cyclohaler (trademark), or in a foil blister in an Aspirair (trademark) device.

The emitted dose (ED) is the total mass of the active agent emitted from the device following actuation. It does not include the material left on the internal or external surfaces of the device, or in the metering system including, for example, the capsule or blister. The ED is measured by collecting the total emitted mass from the device in an apparatus frequently identified as a dose uniformity sampling apparatus (DUSA), and recovering this by a validated quantitative wet chemical assay.

The fine particle dose (FPD) is the total mass of active agent which is emitted from the device following actuation which is present in an aerodynamic particle size smaller than a defined limit. This limit is generally taken to be 5μm if not expressly stated to be an alternative limit, such as 3μm, 2μm or 1μm, etc. The FPD is measured using an impactor or impinger, such as a twin stage impinger (TSI), multi-stage impinger (MSI), Andersen Cascade Impactor or a Next Generation Impactor (NGI). Each impactor or impinger has a pre-determined aerodynamic particle size collection cut points for each stage. The FPD value is obtained by interpretation of the stage-by-stage active agent recovery quantified by a validated quantitative wet chemical assay where either a simple stage cut is used to determine FPD or a more complex mathematical interpolation of the stage-by-stage deposition is used.

The fine particle fraction (FPF) is normally defined as the FPD divided by the ED and expressed as a percentage. Herein, the FPF of ED is referred to as FPF(ED) and is calculated as FPF(ED) = (FPD/ED) x 100%.

The fine particle fraction (FPF) may also be defined as the FPD divided by the MD and expressed as a percentage. Herein, the FPF of MD is referred to as FPF(MD), and is calculated as FPF(MD) = (FPD/MD) x 100%.

The tendency of fine particles to agglomerate means that the FPF of a given dose is highly unpredictable and a variable proportion of the fine particles will be administered to the lung, or to the correct part of the lung, as a result.

In an attempt to improve this situation and to provide a consistent FPF and FPD, dry powder formulations often include additive material.

The additive material is intended to decrease the cohesion between particles in the dry powder formulation. It is thought that the additive material interferes with the weak bonding forces between the small particles, helping to keep the particles separated and reducing the adhesion of such particles to one another, to other particles in the formulation if present and to the internal surfaces of the inhaler device. Where agglomerates of particles are formed, the addition of particles of additive material decreases the stability of those agglomerates so that they are more likely to break up in the turbulent air stream created on actuation of the inhaler device, whereupon the particles are expelled from the device and inhaled. As the agglomerates break up, the active particles return to the form of small individual particles which are capable of reaching the lower lung.

In the prior art, dry powder formulations are discussed which include distinct particles of additive material (generally of a size comparable to that of the fine active particles). In some embodiments, the additive material may form a coating, generally a discontinuous coating, on the active particles and/or any carrier particles.

Preferably, the additive material is an anti-adherent material and it will tend to reduce the cohesion between particles and will also prevent fine particles becoming attached to the inner surfaces of the inhaler device. Advantageously, the additive material is an anti-friction agent or glidant and will give better flow of the pharmaceutical composition in the inhaler. The additive materials used in this way may not necessarily be usually referred to as anti-adherents or anti-friction agents, but they will have the effect of decreasing the cohesion between the particles or improving the flow of the powder. The additive materials are often referred to as force control agents (FCAs) and they usually lead to better dose reproducibility and higher fine particle fractions.

Therefore, an FCA, as used herein, is an agent whose presence on the surface of a particle can modify the adhesive and cohesive surface forces experienced by that particle, in the presence of other particles. In general, its function is to reduce both the adhesive and cohesive forces.

In general, the optimum amount of additive material to be included in a dry powder formulation will depend on the chemical composition and other properties of the additive material and of the active material, as well as upon the nature of other particles such as carrier particles, if present. In general, the efficacy of the additive material is measured in terms of the fine particle fraction of the composition.

Known additive materials usually consist of physiologically acceptable material, although the additive material may not always reach the lung. For example, where the additive particles are attached to the surface of carrier particles, they will generally be deposited, along with those carrier particles, at the back of the throat of the user.

In a further attempt to improve this situation and to provide a consistent FPF and FPD, dry powder formulations often include coarse carrier particles of excipient material mixed with fine particles of active material. Rather that sticking to one another, the fine active particles tend to adhere to the surfaces of the coarse carrier particles whilst in the inhaler device, but are supposed to release and become dispersed upon actuation of the dispensing device and inhalation into the respiratory tract, to give a fine suspension. The carrier particles preferably have MMADs greater than 90μm.

The inclusion of coarse carrier particles is also very attractive where very small doses of active agent are dispensed. It is very difficult to accurately and reproducibly dispense very small quantities of powder and small variations in the amount of powder dispensed will mean large variations in the dose of active agent where the powder comprises mainly active particles. Therefore, the addition of a diluent, in the form of large excipient particles will make dosing more reproducible and accurate.

Carrier particles may be of any acceptable excipient material or combination of materials. For example, the carrier particles may be composed of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously, the carrier particles are of a polyol. In particular, the carrier particles may be particles of crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are of lactose.

Advantageously, substantially all (by weight) of the carrier particles have a diameter which lies between 20μm and 1000μm, more preferably 50μm and 1000μm. Preferably, the diameter of substantially all (by weight) of the carrier particles is less than 355μm and lies between 20μm and 250μm.

Preferably at least 90% by weight of the carrier particles have a diameter between from 60μm to 180μm. The relatively large diameter of the carrier particles improves the opportunity for other, smaller particles to become attached to the surfaces of the carrier particles and to provide good flow and entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lower lung.

The ratios in which the carrier particles (if present) and composite active particles are mixed will, of course, depend on the type of inhaler device used, the type of active particles used and the required dose. The carrier particles may be present in an amount of at least 50%, more preferably 70%, advantageously 90% and most preferably 95% based on the combined weight of the composite active particles and the carrier particles.

However, a further difficulty is encountered when adding coarse carrier particles to a composition of fine active particles and that difficulty is ensuring that the fine particles detach from the surface of the large particles upon actuation of the delivery device.

The step of dispersing the active particles from other active particles and from carrier particles, if present, to form an aerosol of fine active particles for inhalation is significant in determining the proportion of the dose of active material which reaches the desired site of absorption in the lungs. In order to improve the efficiency of that dispersal it is known to include in the composition additive materials, including FCAs of the nature discussed above. Compositions comprising fine active particles and additive materials are disclosed in WO 97/03649 and WO 96/23485.

In light of the foregoing problems associated with known dry powder formulations, even when including additive material and/or carrier particles, it is an aim of the present invention to provide dry powder compositions which have physical and chemical properties which lead to an enhanced FPF and FPD. This leads to greater dosing efficiency, with a greater proportion of the dispensed active agent reaching the desired part of the lung for achieving the required therapeutic effect.

In particular, the present invention seeks to optimise the preparation of particles of active agent used in the dry powder composition by engineering the particles making up the dry powder composition and, in particular, by engineering the particles of active agent. Furthermore, cohesion between particles is to be reduced in order to enhance the FPF and FPD of the dry powder compositions. This is done by preparing the heparin particles in the presence of an FCA.

Whilst the FPF and FPD of a dry powder formulation are dependent on the nature of the powder itself, these values are also influenced by the type of inhaler used to dispense the powder. For example, the FPF obtained using a passive device will tend not to be as good as that obtained with the same powder but using an active device, such as an Aspirair (trade mark) device (see WO 01/00262 and GB 2 353 222).

It is an aim of the present invention to optimise the powder properties, so that the FPF and FPD are improved compared to those obtained using known powder

formulations, regardless of the type of device used to dispense the composition of the invention.

According to a first aspect of the invention, a pharmaceutical composition comprising heparin is provided, wherein the composition is a dry powder for administration by inhalation.

In one preferred embodiment, the heparin is a high molecular weight fraction of heparin.

In another preferred embodiment, the heparin comprises a heparin analogue or derivative. Preferably, the heparin is sulphated heparin.

In another preferred embodiment, the dry powder composition has an FPF of at least 50%. Preferably, the FPF(ED) will be between 70 and 99%, more preferably between 80 and 99%.

In another embodiment, the FPF(MD) is at least 50%. Preferably, the FPF(MD) will be between 50 and 90%, more preferably between 60 and 70%.

In a particularly preferred embodiment, the pharmaceutical composition comprises heparin and a force control agent, the force control agent preferably being present on the surface of particles of heparin.

The preferred FCAs to be included in the compositions of the invention may be any of the additive materials discussed above. Preferably, the FCA is selected from amino acids, peptides and polypeptides having a molecular weight of between 0.25 and 1000 kDa and derivatives thereof, dipolar ions such as zwitterions, phospholipids such as lecithin, and metal stearates such as magnesium stearate. Particularly preferred are amino acids and especially leucine, lysine and cysteine, with leucine being the most preferred.

Known FCAs usually consist of physiologically acceptable material, although the FCA may not always reach the lung. For example, where the FCA particles are attached to the surface of carrier particles, they will generally be deposited, along with those carrier particles, at the back of the throat of the user.

Preferably, the FCAs used in the present invention are film-forming agents, fatty acids and their derivatives, lipids and lipid-like materials, and surfactants, especially solid surfactants.

Advantageously, the FCA includes one or more compounds selected from amino acids and derivatives thereof, and peptides and derivatives thereof. Amino acids, peptides and derivatives of peptides are physiologically acceptable and give acceptable release of the active particles on inhalation.

It is particularly advantageous for the FCA to comprise an amino acid. The FCA may comprise one or more of any of the following amino acids: leucine, isoleucine, lysine, cysteine, valine, methionine, and phenylalanine. The FCA may be a salt or a derivative of an amino acid, for example aspartame or acesulfame K. Preferably, the FCA consists substantially of an amino acid, more preferably of leucine, advantageously L-leucine. The D-and DL-forms may also be used. As indicated above, L-leucine has been found to give particularly efficient dispersal of the active particles on inhalation.

The FCA may include one or more water soluble substances. This helps absorption of the substance by the body if the FCA reaches the lower lung. The FCA may include dipolar ions, which may be zwitterions.

Alternatively, the FCA may comprise a phospholipid or a derivative thereof. Lecithin has been found to be a good material for use as an FCA.

The FCA may comprise a metal stearate, or a derivative thereof, for example, sodium stearyl fumarate or sodium stearyl lactylate. Advantageously, the FCA comprises a metal stearate. For example, zinc stearate, magnesium stearate, calcium

stearate, sodium stearate or lithium stearate. Preferably, the FCA comprises magnesium stearate.

The FCA may include or consist of one or more surface active materials, in particular materials that are surface active in the solid state. These may be water soluble or able to form a suspension in water, for example lecithin, in particular soya lecithin, or substantially water insoluble, for example solid state fatty acids such as oleic acid, lauric acid, palmitic acid, stearic acid, erucic acid, behenic acid, or derivatives (such as esters and salts) thereof, such as glyceryl behenate. Specific examples of such materials are: phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositol and other examples of natural and synthetic lung surfactants; lauric acid and its salts, for example, sodium lauryl sulphate, magnesium lauryl sulphate; triglycerides such as Dynsan 118 and Cutina HR; and sugar esters in general. Alternatively, the FCA may be cholesterol or natural cell membrane materials, including pollen or spore cell wall components such as sporo-pollenins.

Other possible FCAs include sodium benzoate, hydrogenated oils which are solid at room temperature, talc, titanium dioxide, aluminium dioxide, silicon dioxide and starch.

In embodiments, a plurality of different FCAs can be used.

Co-Spray Drying Heparin and Force Control Agents

Spray drying is a well-known and widely used technique for producing particles of material. To briefly summarise, the material to be made into particles is dissolved or dispersed in a liquid or can be made into a liquid which is sprayed through a nozzle under pressure to produce a mist or stream of fine droplets. These fine droplets are usually exposed to heat which evaporates the moisture almost simultaneously, leaving a dry powder.

According to a second aspect of the present invention, the spray drying process involves co-spray drying heparin with one or more force control agents.

The combination or blend of heparin and FCA which is spray dried to form a dry powder formulation can be a solution or suspension in a host liquid. In embodiments, all or at least a proportion of the heparin and/or FCA is or are in solution in the host liquid before being subjected to spray drying. Substantially all of the heparin and FCA can be in solution in the host liquid before being subjected to spray drying.

The heparin is preferably at least 1.5, 2, 4 and, more preferably, at least 10 times more soluble than the FCA in the host liquid at the spraying temperature and pressure. In preferred embodiments, this relationship exists at a temperature between 30 and 60°C and atmospheric pressure. In other embodiments, this relationship exists at a temperature between 20 to 30°C and atmospheric pressure, or, preferably, at 20°C and atmospheric pressure.

Additionally, it is preferred that the heparin is spray dried using a spray drier comprising a means for producing droplets moving at a controlled velocity and of a predetermined size. The advantages of this control of the droplet formation will be discussed in greater detail below.

Finally, the spray drying process may also include a further step wherein the moisture content of the spray dried particles is adjusted, in order to "fine-tune" the properties of the particles.

The effects of adjusting and adapting the spray drying process are illustrated in the experiments discussed below.

Spray drying is a widely used technique and many types of spray drying apparatus are known. The process is relatively cheap and simple. A standard method for producing particles of an active material involves using a conventional spray dryer, such as a Büchi B-191 under a "standard" set of parameters. Such standard parameters are set out in Table 1.

Table 1: "Standard" parameters used in spray drying using the Büchi B-191 spray dryer (Büchi two fluid nozzle, internal setting, 0.7mm mixing needle and cap, 100% aspirator setting).

Atomisation pressure	Inlet temp	Outlet temp	Total solid conc'n (% w/w)	Solvent	Feed rate (ml/min)
5 - 6 bar	150°C	~100°C	1	Aqueous	5

Unless otherwise indicated, the FPF and FDP figures given in the following sections of this specification were obtained by firing capsules, filled with approximately 20 mg of material, from a Monohaler into a multi stage liquid impinger (MSLI), at a flow rate of 90 lpm, or a twin stage or rapid twin stage impinger (TSI or rTSI) at 60 lpm. The "delivered dose" or "DD", which is referred to in some of the following sections, is the same as the emitted dose or ED (as defined above).

Experiment 1

Firstly, the effect of adjusting the solid concentration of heparin was investigated. Heparin was spray dried using the standard parameters as shown in Table 1 but the solid concentration was increased from 1 to 2% w/w, and 5% w/w total solids. The effects of these changes on the FPFs were then investigated and the results were as follows.

Table 2: FPF (%) less than 5µm of the delivered dose (DD) for spray dried heparin using "standard" spray drying parameters

Description	Test	FPF <5µm (DD) (%)
1% w/w heparin	MSLI	17.0
1% w/w heparin	TSI	20.3

The FPF for heparin spray dried alone, that is, without a co-spray dried FCA, using the "standard" spray drying parameters (see Table 1) was 17-20% as shown in Table 2. Testing was done with both a multi stage liquid impinger (MSLI) and a twin stage impinger (TSI).

Table 3: FPF (%) less than 5μm of DD for heparin spray dried from increasing solid concentrations

Description	Test	FPF <5μm (DD) (%)
2% w/w heparin	rTSI	21.3
5% w/w heparin	rTSI	8.3

Increasing the solid concentration of heparin from 1% w/w (Table 2) to 5% w/w (Table 3) caused a large reduction in FPF of heparin; from approximately 20% FPF to 8.3%. 2% w/w solid content did not seem to have an effect on FPF. Testing was done using a rapid-TSI.

Thus, increasing the solid content of the feed solution did not improve the FPF of the heparin particles. Increasing the solid content as high as 5% w/w reduced the FPF by more than 10%. Increasing the solid content of a feedstock without changing any of the other parameters generally causes an increase in particle size, as each droplet will have a greater mass of solid which needs to dry in the same amount of time.

Accordingly, although a solid content of up to 10 % w/w active agent, and in some cases as much as 25% w/w active agent, can be used, it is preferred for up 5%w/w, and more preferably 2 % w/w active agent to be used in the spray drying process of the present invention. It is also preferred for at least 0.05, more preferably 0.5 % w/w to be employed.

Experiment 2

The effects of co-spray drying heparin with varying amounts of l-leucine from aqueous solution were then studied. Standard Büchi spray drying parameters were used, as shown in Table 1. L-leucine was included in the solution of heparin such that the percentage of l-leucine ranged from 2-50% w/w. The results are set out in Table 4.

Table 4: FPF (%) less than 5μm of DD for heparin co-spray dried with l-leucine.

Spray drying feedstock % w/w heparin	Co-spray drying with l-leucine % w/w	Test	FPF <5μm (DD) (%)
1	2%	rTSI	20.0
1	5%	MSLI	32.8
1	10%	MSLI	30.8
1	25%	MSLI	35.4
1	50%	MSLI	51.7

The results show that increasing the percentage of l-leucine included in the feedstock for spray drying resulted in a steady improvement in FPF from approximately 20% FPF with 2% leucine, to 50% FPF with 50% leucine (Table 4). Increasing the percentage of l-leucine also affected surface morphology of the heparin particles and this is discussed below in connection with SEMs of the spray dried particles.

Thus, it has been found that co-spray drying heparin with an FCA leads to significant changes in the particle cohesion, greatly enhancing the properties of the dry powder when administered by pulmonary inhalation. It has also been discovered that the changes to the FPF and FPD are, to an extent, dependent upon the amount of FCA being co-spray dried.

The particles produced in this way will comprise both heparin and the FCA and so the FCA will actually be administered to the lower respiratory tract or deep lung upon inhalation of the dry powder composition. This is in contrast to the additive material used in the prior art, which often was not administered to the deep lung, for example because it remains attached to the large carrier particles.

The amino acids lysine and cysteine, and in particular l-lysine and l-cysteine are especially useful FCAs as a result of this, because it has been discovered that they are mucolytic agents themselves. Thus, their administration to the lung will assist heparin in alleviating the symptoms of the pulmonary diseases, as discussed above.

According to a preferred embodiment of the invention, the active agent is spray dried with from 0.1 to 50% w/w of an FCA, preferably less than 10% w/w of an FCA, and more preferably less than 5% w/w of an FCA.

Experiment 3

Next, the effect of spray drying heparin with various excipients was investigated. Standard spray drying parameters as shown in Table 1 were used and the various excipients tested included lactose, dextrose, mannitol and human serum albumin (HSA). The excipients were co-spray dried with heparin from aqueous solution. From 5 to 50% w/w of the excipients were included, with total solid content not exceeding 1% w/w of the solution.

Table 5: FPF (%) less than 5μm of DD for heparin co-spray dried with excipients.

Spray drying feedstock % w/w	Co-spray drying excipient % w/w	Test	FPF <5μm (DD) (%)
1	5% lactose	RTSI	7.0
1	20% lactose	rTSI	5.3
1	50% lactose	rTSI	10.3
1	5% dextrose	rTSI	11.0
1	50% dextrose	rTSI	1.7
1	5% mannitol	rTSI	14.0
1	20% mannitol	rTSI	11.3
1	5% HSA	rTSI	34.0
1	50% HSA	rTSI	28.0

Inclusion of lactose, dextrose or mannitol did not improve FPF (Table 5). In fact, for all of these excipients, FPFs fell to below the "standard" 20% for spray drying heparin. However, inclusion of 5% HSA gave an improvement of approximately 15%.

As the presence of the HSA in the active particle clearly reduces the particle cohesion and thereby increases the FPF, HSA is considered, for the purpose of the present invention, to be an FCA. However, as co-spraying heparin with lactose,

dextrose or mannitol did not increase the FPF, these excipients are not considered to be FCAs.

According to another embodiment of the present invention, the active agent is co-spray dried with HSA. Preferably, the active agent is co-spray dried with up to 50% w/w HSA, and more preferably with less than 10% % w/w of HSA and most preferably with less than 5% w/w of HSA. In another embodiment of the present invention, the FCA is not HSA.

Alternative FCAs which could be co-spray dried with the heparin include phospholipids and lecithins. However, heparin is insoluble in organic solvents, whilst lecithin is insoluble in an aqueous phase. Therefore, in order to co-spray dry heparin with lecithin or other water insoluble FCAs, one must use a technique such as hydrophobic ion pairing.

Experiment 4

This experiment sought to evaluate the effect of spray drying heparin with various organic solvents. The "standard" parameters as outlined in Table 1 were used to spray dry heparin, with the only difference being that the heparin was spray dried from 10% w/w organic solvent (selected from propan-1-ol, methanol and ethanol) in water. The results are set out in Table 6.

Table 6: FPF (%) less than 5µm of DD for heparin spray dried from an organic solvent.

Spray drying feedstock % w/w heparin	Solvent % w/w	Test	FPF <5µm (DD) (%)
1	10 % methanol	MSLI	2.3
1	10% ethanol	MSLI	6.2
1	10% propan-1-ol	MSLI	2.0

Spray drying 1% w/w heparin from 10% methanol, ethanol and propan-1-ol resulted in a lowering of FFP (Table 6) from approximately 20% when spray dried from aqueous solvent using identical parameters (Table 2) to 2-6% FPF.

One might expect adding an organic solvent to the feedstock would cause an increase of the FPF, as a result of a reduction in the viscosity of the feedstock, and a lower energy input being required to generate smaller particles. However, the FPFs obtained by 2-fluid nozzle spray drying of heparin from feedstocks containing 10% organic solvent (Table 6) were actually reduced. However, whilst it may not be desirable to spray dry heparin with propan-1-ol, methanol or ethanol, the results obtained for these co-solvents show that they could be used when an additive or FCA that is insoluble in water is to be spray dried with the heparin.

Experiment 5

As a further test, heparin was spray dried using the standard parameters used above (Table 1), but effect of temperature on the particles produced was investigated by spray drying with inlet temperatures of 75°C and 220°C. The results are set out in Table 7.

Table 7: FPF (%) less than 5µm of DD for heparin spray dried using different inlet temperatures.

Inlet temperature	Approx. Outlet temperature	Test	FPF <5µm (DD) (%)
220°C	135°C	MSLI	17.5
75°C	35°C	rTSI	22.5

Thus, it can be seen that spray drying heparin at a higher or lower inlet temperature relative to the "standard" 150°C normally used did not offer a substantial improvement in FPF. Indeed, variations in the inlet temperature appeared to have little, if any, effect.

A preferable range for the inlet temperature is 40°C to 300°C, preferably 75°C to 220°C. A preferable range for the outlet temperature is 20°C to 200°C, preferably 35°C to 135°C.

From these experiments and results it can be seen that the co-spray drying of heparin with an FCA resulted in the greatest increase in FPF and that this increase was quite marked.

In view of this increased FPF and FPD, it may even be possible to do away with the large carrier particles in a dry powder comprising heparin which has been co-spray dried with a force control agent. However, it may still be desirable to include carrier particles, especially where the heparin is to be administered in small amounts, as the bulk of the larger carrier particles will help to ensure that an accurate dose is dispensed.

In one embodiment of the present invention, the pharmaceutical composition comprises fine particles of heparin and carrier particles having a particle size of at least 20μm. Preferably, the carrier particles are composed of any acceptable excipient material or combination of materials. For example, the carrier particles are composed of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously, the carrier particles are of a polyol. In particular, the carrier particles may be particles of crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are of lactose.

It has further been discovered that the FPF and FPD of the dry powder formulation is also affected by the means used to create the droplets which are spray dried. Different means of forming droplets can affect the size and size distribution of the droplets, as well as the velocity at which the droplets travel when formed and the gas flow around the droplets. In this regard, the velocity at which the droplets travel when formed and the gas (which is usually air) flow around the droplets can dramatically affect size, size distribution and shape of resulting dried particles.

According to a second aspect of the invention, a method of preparing a dry powder composition is provided, wherein the heparin is spray dried using a spray drier comprising a means for producing droplets moving at a controlled velocity and of a predetermined droplet size. The velocity of the droplets is preferably controlled relative to the body of gas into which they are sprayed. This can be achieved by

controlling the droplets' initial velocity and/or the velocity of the body of gas into which they are sprayed.

It is clearly desirable to be able to control the size of the droplet formed during the spray drying process and the droplet size will affect the size of the dried particle. Preferably, the droplet forming means also produces a relatively narrow droplet, and therefore particle, size distribution. This will lead to a dry powder formulation with a more uniform particle size and thus a more predictable and consistent FPF and FPD.

The ability to control the velocity of the droplet also allows further control over the properties of the resulting particles. In particular, the gas speed around the droplet will affect the speed with which the droplet dries. In the case of droplets which are moving quickly, such as those formed using a 2-fluid nozzle arrangement (spraying into air), the air around the droplet is constantly being replaced. As the solvent evaporates from the droplet, the moisture enters the air around the droplet. If this moist air is constantly replaced by fresh, dry air, the rate of evaporation will be increased. In contrast, if the droplet is moving through the air slowly, the air around the droplet will not be replaced and the high humidity around the droplet will slow the rate of drying. As discussed below in greater detail, the rate at which a droplet dries affects various properties of the particles formed, including FPF and FPD.

Preferably the velocity of droplets at 10 mm from their point of generation is less than 100 m/s, more preferably less than 50 m/s, most preferably less than 20 m/s. Preferably the velocity of the gas, used in the generation of the droplets, at 10 mm from the point at which they are generated is less than 100 m/s, more preferably less than 50 m/s, most preferably less than 20 m/s. In an embodiment, the velocity of the droplets relative to the body of gas into which they are sprayed, at10 mm from their point of generation, is less than 100 m/s, more preferably less than 50 m/s, most preferably less than 20 m/s.

Preferably, the means for producing droplets moving at a controlled velocity and of a predetermined size is an alternative to the commonly used 2-fluid nozzle. In one embodiment, an ultrasonic nebuliser (USN) is used to form the droplets in the spray drying process.

Whilst ultrasonic nebulisers (USNs) are known, these are conventionally used in inhaler devices, for the direct inhalation of solutions containing drug, and they have not previously been widely used in a spray drying apparatus. However, it has been discovered that the use of such a nebuliser in spray drying has a number of important advantages and these have not previously been recognised.

USNs use an ultrasonic transducer which is submerged in a liquid. The ultrasonic transducer (a piezoelectric crystal) vibrates at ultrasonic frequencies to produce the short wavelengths required for liquid atomisation. In one common form of USN, the base of the crystal is held such that the vibrations are transmitted from its surface to the nebuliser liquid, either directly or via a coupling liquid, which is usually water. When the ultrasonic vibrations are sufficiently intense, a fountain of liquid is formed at the surface of the liquid in the nebuliser chamber. Large droplets are emitted from the apex and a "fog" of small droplets is emitted. A schematic diagram showing how the USN works is shown in Figure 1.

The attractive characteristics of USNs for producing fine particle dry powders include: low spray velocity; the small amount of carrier gas required to operate the nebulisers; the small droplet size and narrow droplet size distribution produced; the simple nature of the USNs (the absence of moving parts which can wear, etc.); and the ability to accurately control the gas flow around the droplets, thereby controlling the rate of drying.

To elaborate, USNs do not separate the liquid into droplets by increasing the velocity of the liquid. Rather, the necessary energy is provided by the vibration caused by the ultrasonic nebuliser.

Thus, as an alternative to the conventional Büchi two-fluid nozzle, an ultrasonic nebuliser (Mini Humidifier) may be used to generate droplets of active agent, which are then dried within the Büchi drying chamber. In one arrangement, the USN is placed in the feed solution comprising an active agent in a specially designed glass chamber which allows introduction of the cloud of droplets generated by the USN directly into the heated drying chamber of the spray dryer.

The two-fluid nozzle is left in place to seal the hole in which it normally sits, but the compressed air was not turned on. The drying chamber is then heated up to 150°C inlet temperature, with 100% aspirator setting. Due to the negative pressure of the Büchi system, the nebulised cloud of droplets is easily drawn in to the drying chamber, where the droplets are dried to form particles, which are subsequently classified by the cyclone, and collected in the collection jar. It is important that the level of feed solution in the chamber is regularly topped up to avoid over concentration of the feed solution as a result of continuous nebulisation.

In an embodiment of the present invention, the method of preparing the active particles involves the use of an ultrasonic nebuliser. Preferably, the ultrasonic nebuliser is incorporated in a spray drier.

Two theories have been developed which describe the mechanism of liquid disintegration and aerosol production in ultrasonic devices (Mercer 1981, 1968 and Sollner 1936). Lang (1962) observed that the mean droplet size generated from thin liquid layers was proportional to the capillary wavelength on the liquid surface. Using the experimentally determined factor of 0.34, the droplet diameter D is given by:

$$d_p = 0.34\ (8\pi\gamma/pf^2)^{1/3}$$

p = solution density g cm^{-3} (water = 1)

γ = surface tension dyn cm^{-1} (water = 70)

f = frequency (MHz)

This means that for a frequency of 1.7 MHz the calculated droplet size is 2.9μm and for 2.4 MHz the calculated droplet size is 2.3μm. Atomisers are also available with frequencies up to 4 MHz, with a calculated droplet size of 1.6 μm.

Clearly, this allows the size of the droplets to be accurately and easily controlled, which in turn means that the active particle size can also be controlled (as the dried particle size will depend, to a great extent, on the size of the droplet).

Experiment 6

A USN was used to prepare dry powders using a feed solution of heparin alone and of a blend of heparin and 1% to 5% and 10% w/w leucine. The ultrasonic nebuliser feed flow rate was 130 ml/hr. The furnace temperature of the nebulised powders was set at 350°C. Figure 2 shows a schematic drawing of the ultrasonic set-up.

In order to test the processing of the powders, work was conducted using a Monohaler and capsules filled with 20mg of powder and fired into a rapid TSI in the manner previously explained. The study used a TSI flow rate of 60lpm with a cut-off of approximately 5μm.

The rapid TSI results using the dry powder produced using the USN indicate a low aerosolisation efficiency for pure heparin particles, but an improvement was seen in FPF with addition of leucine as a FCA.

Three measurements were made and the results are summarised below in Table 8, giving the average values of the three sets of results obtained.

Table 8: rapid TSI results using the dry powder produced using a USN with varying amounts of FCA

Formulation	FPF% (metered dose)	FPD (mg)
Heparin (0% leucine)	1.1	0.22
Heparin + leucine (1% w/w)	17.4	3.5
Heparin + leucine (2% w/w)	30.2	6.0
Heparin + leucine (3% w/w)	28.6	5.7

Heparin + leucine (4% w/w)	48.4	9.7
Heparin + leucine (5% w/w)	41.5	8.3
Heparin + leucine (10% w/w)	55.8	11.8

Experiment 7

Then, in order to establish the effect of secondary drying of the dry powders, samples of heparin alone and heparin + leucine (10% w/w) were secondary dried at 50°C under vacuum for 24 hours.

The results set out in Table 9 indicate the secondary drying step further raised the FPF and FPD.

Table 9: rapid TSI results using the dry powder produced using a USN with varying amounts of FCA, after secondary drying

Formulation	FPF% (metered dose)	FPD (mg)
Heparin (0% leucine)	4.1	0.82
Heparin + leucine (10% w/w)	70.8	14.2

Experiment 8

In order to allow comparison of the powder prepared using a USN with powders produced using a conventional spray drying technique, 1% total solids solution was sprayed from a 2-fluid nozzle into a Büchi spray drier. Blends of heparin and leucine were prepared at different weight percentages of leucine. Powders with 2%, 5%, 10%, 25% and 50% w/w leucine were prepared. The spray drier feed flow rate was 120 ml/hr, the inlet temperature was 150°C, and flush nozzle setting was used. The schematic set-up of the two-fluid nozzle spray drier is shown in Figure 3.

In a first MSLI study, an internal nozzle alignment was used and the powder was not subjected to a secondary drying process. The feed rate used was 300 ml/hr.

20 mg of powder was dispersed in each case and the results set out in Table 10 indicate an improvement of FPF with addition of a FCA, although the FPD does

not improve with the addition of more than 10% leucine due to the relative reduction of the heparin content.

Table 10: MSLI study of co-spray dried heparin and varying concentrations of leucine

Formulation	Test	ED (mg)	FPF% (emitted dose)	FPD (mg)
Heparin (0% leucine)	MSLI	10	17	1.8
Heparin + leucine (5% w/w)	MSLI	11	33	3.6
Heparin + leucine (10% w/w)	MSLI	13	31	3.9
Heparin + leucine (25% w/w)	MSLI	10	35	3.7
Heparin + leucine (50% w/w)	MSLI	6	52	3.0

Thus, in preferred embodiments, the heparin is spray dried with from 0.1 to 50% w/w FCA to heparin, preferably from 1 to 10% w/w FCA to heparin, and more preferably less than 5% w/w FCA to heparin. An added advantage of employing the preferred amounts of FCA is that the risk of toxicity problems is reduced.

In further preferred embodiments, the FCA is an amino acid, and more preferably the FCA is one or more of leucine, preferably l-leucine, isoleucine, lysine and cysteine. Most preferably, the heparin is co-spray dried with l-leucine.

Experiment 9

In a particle size study, the particle size of the spray dried particles formed using the USN was analysed. The dry powders were dispersed at 4 Bar in a Helos disperser. The values of FPF <5μm and D10, D50 and D90 of the ultrasonic nebulised powders were measured and are indicated in Table 12 (10% by volume of the particles are of a size, measured by Malvern, that is below the D10 value. 50% by volume of the particles are of a size, measured by Malvern, that is below the D50 value and so on). The values are an average of three measurements.

Table 12: Particle size study of spray dried particles using USN, without secondary drying

Formulation	D10	D50	D90	FPF% (<5μm)
Heparin (0% leucine)	0.43	1.07	4.08	90.52
Heparin + leucine (1% w/w)	0.41	0.90	1.79	99.97
Heparin + leucine (2% w/w)	0.41	0.89	1.75	100
Heparin + leucine (3% w/w)	0.41	0.88	1.71	100
Heparin + leucine (4% w/w)	0.41	0.86	1.71	100
Heparin + leucine (5% w/w)	0.41	0.90	1.84	100
Heparin + leucine (10% w/w)	0.41	0.89	1.76	100

Figure 6 shows a typical size distribution curve of three repeated tests of pure heparin powder generated using an ultrasonic nebuliser. The main peak represents the size of the individual active particles, ranging between 0.2μm and 4.5μm in diameter. The second, smaller peak between diameters of 17 to 35μm represents agglomerates of active particles.

Sympatec particle sizing (Helos dry dispersed) results showed that ultrasonic nebulised powders have a narrower size distribution and smaller mean particle size than the 2-fluid nozzle spray dried powders.

Experiment 10

The foregoing particle size tests were also conducted on secondary dried powders and the results can be seen in Table 13. The dry powders were dispersed at 4bar in a Helos disperser. The powders were secondary dried over 24 hours under vacuum.

Table 13: Particle size study of spray dried particles using USN, after secondary drying

Formulation	D10	D50	D90	FPF% (<5μm)
Heparin (0% leucine)	0.44	1.06	2.93	92.35
Heparin + leucine (10% w/w)	0.40	0.87	1.77	100

Thus, one can see that the secondary dried powder did not reveal any significant difference in particle size, both for heparin alone and a blend of heparin and leucine.

Figure 5 shows a comparison between particle size distribution curves of secondary dried and not secondary dried powders. The powder used was heparin with 10% leucine w/w. Clearly, there is virtually no difference between the curves, illustrating that secondary drying does not have an effect on particle size.

Experiment 11

Then, in order to establish whether the effect of secondary drying varied between particles produced using a USN and a 2-fluid nozzle, the particle size study of secondary drying with spray dried particles formed using the USN was repeated but using a 2-fluid nozzle spray drier. Once again, the powders were secondary dried over 24 hours under vacuum. Values of FPF <5μm and D10, D50 and D90 of the spray dried powders are indicated in Table 14 below.

Table 14: Particle size study of 2-fluid nozzle spray dried particles after secondary drying

Formulation	D10	D50	D90	FPF% (<5μm)
Heparin + leucine (2% w/w)	0.59	2.09	5.19	89.57
Heparin + leucine (5% w/w)	0.61	2.16	4.77	91.18
Heparin + leucine (10% w/w)	0.58	2.04	3.93	96.6
Heparin + leucine (25% w/w)	0.63	2.34	4.85	91.15
Heparin + leucine (50% w/w)	1.05	3.03	6.62	80.03

Figure 6 shows three repeated size distribution curve of heparin with 5% leucine w/w powder generated by the 2-fluid nozzle spray drier.

Thus, it can be seen that particles formed using a spray drying process involving an ultrasonic nebuliser have been found to have a greater FPF than those produced using a standard spray drying apparatus, for example with a two nozzle configuration.

Turning now to the morphology of the generated powders, it has been discovered that the shape of particles formed by co-spray drying heparin and leucine using a

conventional 2-fluid nozzle spray drying technique differs to that of particles formed by co-spray drying heparin and leucine using an ultrasonic nebuliser.

The morphology of the particles was viewed using scanning electron micrographs (SEMs). A sample preparation for this is set out below.

Pieces of double-sided carbon tape were placed on a numbered planchette. The backing was removed and small amounts of samples placed on them (the pieces of carbon tape were identified for different samples where appropriate). The backing was pressed on to ensure firm adherence of the sample to the tape. Excess sample was tapped off. Samples were coated in an Edwards Sputter Coater S150B at HT voltage 7 for an appropriate length of time (approximately 12 minutes).

SEM details: Jeol 6310. 10kV accelerating voltage. Spot size 13. Working distance 15. Noise reduction 20.

SEM micrographs of 2-fluid nozzle spray dried powders (Figures 7a-d) illustrate a clear relationship between the increasing percentage of l-leucine and an increasingly dimpled or wrinkled surface of the particles. The particles with the highest l-leucine content appear to be extremely wrinkled and, in selected cases, are possibly burst as an extreme result of "blowing", a phenomenon whereby the particles form a shell or skin which inflates and then collapses.

Droplets from the two fluid nozzle are initially dried at a relatively high rate during spray drying and this creates a viscous layer of material around the exterior of the liquid droplet. As the drying continues, the viscous layer is firstly stretched (like a balloon) by the increased vapour pressure inside the viscous layer as the solvent evaporates. The solvent vapour diffuses through the growing viscous layer until it is exhausted and the viscous layer then collapses, resulting in the formation of craters in the surface or wrinkling of the particles. The viscosity of the viscous layer has been related to the glass transition temperature of the material by the WLF (Williams, Landel, Ferry) Equation (see Alexander et al, Drying Technology; Vol. 3, No. 3, 1985).

Figure 7a is an SEM micrograph of 2-fluid nozzle spray dried heparin (without secondary drying). The particles are generally spherical in shape and the surfaces are substantially smooth. However, the particles each have one (smooth) crater or dimple in their surface.

Figure 7b is an SEM micrograph of 2-fluid nozzle spray dried heparin with 5% leucine (without secondary drying). The particles now exhibit more dimples or craters on their surface. The particles still have a generally smooth surface.

Figure 7c is an SEM micrograph of 2-fluid nozzle spray dried heparin with 25% leucine (without secondary drying). With the increase in FCA, the surface of the particles no longer appears smooth and the generally spherical shape has disappeared. The particles have a shrivelled, deflated appearance.

Figure 7d is an SEM micrograph of 2-fluid nozzle spray dried heparin with 50% leucine (without secondary drying). The shrivelling observed in the particles of Figure 7c has become more pronounced and the particles appear to have completely collapsed, looking like empty skins or shells.

Figures 7e-h show SEM micrographs of 2-fluid nozzle spray dried heparin with 2, 5, 10 and 50% leucine, after secondary drying. When one compares the particles in these Figures to those in Figures 7a-d, it can be seen that the secondary drying does appear to increase the "collapse" of the particles. Thus, even at low percentages of FCA, the secondary dried particles have a more wrinkled or shrivelled shape.

Thus, where the spray drying takes place using a 2-fluid nozzle, it has been found that spray drying heparin with a FCA leads to an unusual particle morphology. At low concentrations of FCA, the surfaces of the particles show dimples or depressions. As the amount of co-spray dried FCA is increased, these dimples become more extreme, with the particles eventually having a shrivelled or wrinkled surface.

This change in the surface morphology of these co-spray dried particles appeats to reduce the cohesion between the particles. Conventional particles of active material are generally spherical in shape as seen in Figure 7a. This relatively smooth, regular shape of the fine particles means that they are likely to agglomerate, as discussed above. However, less agglomeration is observed as the irregularity of the surface of the co-spray dried particles increases. This suggests that the dimpled or wrinkled surfaces provide less surface area for attraction between the fine particles. It is also speculated that this particle morphology may even help the particles to fly when they are expelled for the inhaler device. This, together with the reduced agglomeration, means that more heparin particles will reach the desired part of the lung in order to provide the required therapeutic effect.

However, the distinctive dimples or wrinkles observed on the surface of the particles prepared by co-spray drying leucine using a 2-fluid nozzle spray drier are not present when the particles are co-spray dried using an ultrasonic nebuliser.

Figure 8a shows SEM micrographs of USN spray dried heparin alone, without secondary drying, whilst Figure 8b shows SEM micrographs of USN spray dried heparin with 10% leucine, also without secondary drying.

As can be clearly seem from the SEMs, the shape of particles formed by co-spray drying an active agent and leucine using a USN differs to that of particles formed by co-spray drying heparin and leucine using a conventional 2-fluid nozzle spray drying technique.

The SEM micrographs of pure heparin generated using a USN show that the particles have a size of approximately 2μm or less. The SEMs also show that these particles tend to form "hard" agglomerates of up to 200μm.

In contrast, the SEMs of nebulised heparin and leucine show that the primary particles produced are of the same size as the pure heparin particles. However, these particles are discrete and agglomerates are not evident.

What is more, the distinctive dimples or wrinkles observed on the surface of the particles prepared by co-spray drying heparin and leucine using a 2-fluid nozzle spray drier (Figures 7a-2d) are not present when the particles are spray dried using a USN. Despite this, the co-spray dried particles formed using a USN still have an improved FPF and FPD over particles formed in the same way but without the FCA. In this case, this improvement is clearly not due to the shape of the particles.

We believe the leucine concentration at the surface of the solid particles is governed by several factors. These include the concentration of leucine in the solution which forms the droplets, the relative solubility of leucine compared to heparin, the surface activity of leucine, the mass transport rate within the drying droplet and the speed at which the droplets dry. If drying is very rapid it is thought that the leucine content at the particle's surface will be lower than that for a slower drying rate. The leucine surface concentration is determined by the rate of leucine transport to the surface, and its precipitation rate, during the drying process.

As mentioned above, high gas flow rates around the droplets can accelerate drying and it is thought that, because the gas flow around droplets formed using a USN is low in comparison to that around droplets formed using conventional 2-fluid nozzles, droplets formed using the former technique dry more slowly than those produced by using conventional 2-fluid nozzles. The leucine (or other FCA) concentration on the shell of droplets and dried particles produced using a USN can be higher as a result. It is considered that these effects reduce the rate of solvent evaporation from the droplets and prevent "blowing" and, therefore, are responsible for the physically smaller and smoother primary particles we have observed (Kodas, T.T and Hampden Smith, M., 1999, Aerosol Processing of materials,440). In this last regard, and as previously noted, droplets formed by the 2-fluid nozzle system have rapid air flow around them and they, therefore, dry very rapidly, and suffer from the effects of blowing.

As already noted, Sympatec particle sizing (Helos dry dispersed) results showed that ultrasonic nebulised powders have a narrower size distribution and smaller mean particle size than the 2-fluid nozzle spray dried powders.

Figure 9a shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 2% leucine w/w.

Figure 9b shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 5% leucine w/w.

Figure 9c shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 10% leucine w/w.

These figures show a gradual disappearance of the second peak, indicating that the incidence of agglomerates is reduced as the amount of co-spray dried FCA is increased.

For the USN, spray dried material, agglomerate peaks disappears under the same test conditions when > 3 % leucine is added. For the 2-fluid nozzle spray dried material, agglomerate peaks disappear under the same test conditions when >10% leucine is added. This indicates that adding leucine as an FCA reduces the strength of the agglomerates in heparin powder. It further suggests that ultrasonic nebulised materials de-agglomerate more easily at lower leucine (FCA) contents. This may be related to the surface concentration of the leucine (FCA), as mentioned above.

The SEM images of ultrasonic nebulised powders (Figures 8a and b) also support the finding that addition of leucine facilitates aerosolisation. SEMs of pure heparin showed that although heparin primary particles are <2μm, large distinct agglomerates are formed. The SEMs of all of the powders comprising heparin and leucine show that the primary particle size is still <2μm, but the large agglomerates are not evident.

It can be seen that particles formed using a spray drying process involving an ultrasonic nebuliser have been found to have a greater FPF than those produced using a standard spray drying apparatus, for example with a two nozzle configuration.

What is more, the particles formed using a spray drying process using a USN have been found to have a narrower particle size distribution than those produced using a standard spray drying apparatus, for example with a two nozzle configuration.

Similar results to those shown above when using USNs are expected for spray drying using other means which produce low velocity droplets. For example, further alternative nozzles may be used, such as electrospray nozzles or vibrating orifice nozzles. These nozzles, like the ultrasonic nozzles, are momentum free, resulting in a spray which can be easily directed by a carrier air stream.

Another attractive type of nozzle for use in a spray drying process is one which utilises electro-hydrodynamic atomisation. A tailor cone is created at a fine needle by applying high voltage at the tip. This shatters the droplets into an acceptable monodispersion. This method does not use a gas flow, except to transport the droplets after drying. An acceptable monodispersion can also be obtained utilising a spinning disc generator.

The nozzles such as ultrasonic nozzles, electrospray nozzles or vibrating orifice nozzles can be arranged in a multi nozzle array, in which many single nozzle orifices are arranged in a small area and facilitate a high total throughput of feed solution. The ultrasonic nozzle is an ultrasonic transducer (a piezoelectric crystal). If the ultrasonic transducer is located in an elongate vessel the output may be raised significantly.

When active particles are produced by spray drying, some moisture will remain in the particles. This is especially the case where the active agent is temperature sensitive and does not tolerate high temperatures for the extended period of time which would normally be required to remove further moisture from the particles.

The amount of moisture in the particles will affect various particle characteristics, such as density, porosity, flight characteristics, and the like.

Therefore, according to a third aspect of the present invention, a method of preparing a dry powder composition is provided, wherein the method comprises a step of adjusting the moisture content of the particles.

In one embodiment, the moisture adjustment or profiling step involves the removal of moisture. Such a secondary drying step preferably involves freeze-drying, wherein the additional moisture is removed by sublimation. An alternative type of drying is vacuum drying.

Generally, the secondary drying takes place after the active has been co-spray dried with a force control agent. In another embodiment, the secondary drying takes place after nebulised active agent has been spray dried, wherein the active agent was optionally in a blend with a FCA.

The secondary drying step has two particular advantages. Firstly, it can be selected so as to avoid exposing the heparin to high temperatures for prolonged periods. Furthermore, removal of the residual moisture by secondary drying is significantly cheaper than removing all of the moisture from the particle by spray-drying. Thus, a combination of spray drying and freeze-drying or vacuum drying is economical and efficient.

Secondary drying significantly reduces the moisture content of heparin particles (from approximately 8.5% to 2%). This would imply that the heparin is drying in such a way that there is a hard outer shell holding residual moisture, which is driven off by secondary drying, and entrapped moisture is trapped with in a central core. One could infer that the residence time of the particle in the drying chamber is too short, and that the outer shell is being formed rapidly and is too hard to permit moisture to readily escape during the initial spray drying process.

Secondary drying can also be beneficial to the stability of the product, by bringing down the moisture content of a powder. It also means that drugs which may be very heat sensitive can be spray dried at lower temperatures to protect them, and then subjected to secondary drying to reduce the moisture further, and protect the drug.

In another embodiment of the third aspect of the invention, the moisture profiling involves increasing the moisture content of the spray dried particles.

Preferably, the moisture is added by exposing the particles to a humid atmosphere. The amount of moisture added can be controlled by varying the humidity and/or the length of time for which the particles are exposed to this humidity.

From the results presented herein, it can be seen that improvement in the FPF of spray dried active agents can be achieved by using one or more of the following:

1) co-spray drying the active agent with a force control agent;
2) using a means of producing droplets for spray drying which results in slow velocity droplets, the size of which can be accurately controlled; and
3) moisture profiling of the spray dried particles.

The above discussion and experiments focussed on conventional spray drying apparatus and ultrasonic nebulizing apparatus. However, it should be noted that further changes to the apparatus may be made to ensure that the particles collected at the end of the spray drying process have the optimum properties.

For example, the nature of the drying chamber may be changed, to get better drying and/or other advantages. Thus, in one embodiment of the invention, a spray drying apparatus comprising a drying chamber with heated walls may be used. Such drying chambers are known and they have the advantage that the hot walls discourage deposition of the spray dried material on them. However, the heated walls create a temperature gradient within the drying chamber, where the air in the outer area of the chamber is hotter than that in the centre of the chamber. This uneven temperature can cause problems because particles which pass through different

parts of the drying chamber will have slightly different properties as they may well dry to differing extents.

In an alternative embodiment, the spray drying apparatus comprises a radiative heat source in the drying chamber. Such heat sources are not currently used in spray drying. This type of heat source has the advantage that it does not waste energy heating the air in the drying chamber. Rather, only the droplets/particles are heated as they pass through the chamber. This type of heating is more even, avoiding the temperature gradients mentioned above in connection with drying chambers with heated walls. This also allows the particles to dry from inside the droplets thus reducing or avoiding crust forming.

In yet another embodiment, the spray dried particles are collected using a vertical drying column. These columns are already known in spray drying devices and they collect the spray dried particles by carrying the particles up a vertical column using an air flow, rather than simply relying on gravity to collect the particles in a collection chamber. The advantage of using such a vertical drying column to collect the spray dried particles is that it allows for aerodynamic classification of the particles. Fine particles tend to be carried well by the air flow, whilst larger particles are not. Therefore, the vertical drying column does not collect these larger particles.

An alternative process to conventional spray drying is freeze-drying, wherein the substance to be dried, which need not be a liquid, is frozen so that the water contained therein is turned to ice. The ice is then removed by sublimation.

A variation of freeze-drying is spray freeze-drying, wherein a liquid containing a dissolved or dispersed substance is pumped through at least one nozzle to produce a stream of liquid exiting the nozzle causing the continuous stream to break apart, forming droplets. The droplets are then contacted with a cryogenic liquid capable of freezing the droplets into a solid phase. The droplets are concentrated into a portion of the contacting cryogenic liquid from which they are subsequently collected and defrosted.

Freeze-drying a particulate material, such as medicinal drug particles or intermediate products to be used for the manufacture of such particles is described in US Patent No. 4,608,764. In this patent, it is disclosed that a particulate material comprising an active substance is dried in a container in which a gas is passed through the particles. The temperature of the gas is adjusted to have at least a considerable part of the drying operation to take place by sublimation.

Spray-freeze-drying for converting liquid substances into dry powder is described in US Patent No. 5,208,998. According to the reference, a single processing vessel is used to perform a series for steps (freezing, drying, defrosting and resetting) which are executed in a continuous, repetitive cycle. The use of a recirculating gas, such as nitrogen, serves to freeze the sprayed liquid, drying the resulting frozen particles, as assisting the defrosting step.

Other spray-drying techniques are described in the prior art and these can also be used to prepare heparin dry powder formulations in accordance with the present invention, either as they are described, or incorporating some of the adaptations described above. Examples of such other spray drying techniques include those described in patent publications US 6,253,463, US 6,001,336, US 5,260,306, WO 91/16882 and WO 96/09814. Additionally, suitable spray drying techniques are described in the "Spray Dry Handbook", John Wiley & Sons, New York, 1984.

Micronised Heparin

Instead of spray drying the heparin to form a dry powder formulation, it is also possible to use other methods of preparing a dry powder. For example, many dry powders are formed by micronisation, that is, grinding up larger particles to form small particles of a desired size.

Techniques known as co-milling and mechanofusion, as described in detail in International Publication No. WO 02/43701, produce composite active particles and also are suitable for preparing the heparin dry powder formulations of the present invention.

The composite active particles formed by co-milling and mechanofusion in the present invention are very fine particles of heparin which have, upon their surfaces, an amount of an FCA. The FCA is preferably in the form of a coating on the surfaces of the particles of heparin. The coating may be a discontinuous coating. The FCA may be in the form of particles adhering to the surfaces of the particles of heparin. As explained below, at least some of the composite active particles may be in the form of agglomerates.

When the composite active particles are included in a pharmaceutical composition the FCA promotes the dispersal of the composite active particles on administration of that composition to a patient, via actuation of an inhaler, as discussed above. Thus, once again, the presence of the FCA is able to increase the FPF and FPD of the dry powder formulation.

It has also been found that the milling of the particles of heparin in the presence of an FCA produces significantly smaller particles and/or requires less time and less energy than the equivalent process carried out in the absence of the FCA. This allows composite active particles to be produced which have a mass median aerodynamic diameter (MMAD) or a volume median diameter (VMD) of less than 1μm. It is often not possible to make such small particles by other milling methods.

It is known that a milling process will tend to generate and increase the level of amorphous material on the surfaces of the milled particles thereby making them more cohesive. In contrast, the composite heparin of the invention will often be found to be less cohesive after the milling treatment.

The word "milling" as used herein refers to any mechanical process which applies sufficient force to the particles of active material that it is capable of breaking coarse particles (for example, particles of mass medium aerodynamic diameter greater than 100μm) down to fine particles of mass median aerodynamic diameter not more than 50μm or which applies a relatively controlled compressive force as described below in relation to the MechanoFusion and Cyclomix methods.

A high degree of force is required to separate the individual particles of heparin (which tend to agglomerate because of the sticky nature of this active agent) such that effective mixing and effective application of the FCA to the surfaces of those heparin particles is achieved. It is believed that an especially desirable aspect of the milling process is that the FCA may become deformed in the milling and may be smeared over or fused to the surfaces of the heparin particles. It should be understood, however, that in the case where the particles of heparin are already fine, for example, having an MMAD below 20μm prior to the milling step, the size of those particles may not be significantly reduced. The important thing is that the milling process applies a sufficiently high degree of force or energy to the particles.

The method generally involves bringing the particles of FCA into close contact with the surfaces of the heparin particles in order to achieve coated particles. A degree of intensive mixing is required to ensure a sufficient break-up of agglomerates of both constituents, dispersal and even distribution of FCA over the heparin particles.

As a consequence of the milling step, complete or partial, continuous or discontinuous, porous or non-porous coatings may be formed. The coatings originate from a combination of heparin and FCA particles. They are not coatings such as those formed by wet processes that require dissolution of one or both components. In general, such wet coating processes are likely to be more costly and more time consuming than the milling process of the invention and also suffer from the disadvantage that it is less easy to control the location and structure of the coating.

A wide range of milling devices and conditions are suitable for use in the method of the invention. The milling conditions, for example, intensity of milling and duration, should be selected to provide the required degree of force.

Ball milling is a suitable milling method. Centrifugal and planetary ball milling are especially preferred methods. Alternatively, a high pressure homogeniser may be

used in which a fluid containing the particles is forced through a valve at high pressure producing conditions of high shear and turbulence.

Shear forces on the particles, impacts between the particles and machine surfaces or other particles and cavitation due to acceleration of the fluid may all contribute to the fracture of the particles and may also provide a compressive force.

Such homogenisers may be more suitable than ball mills for use in large scale preparations of the composite active particles.

Suitable homogensiers include EmulsiFlex high pressure homogenisers which are capable of pressures up to 4000 Bar, Niro Soavi high pressure homogenisers (capable of pressures up to 2000 Bar), and Microfluidics Microfluidisers (maximum pressure 2750 Bar). The milling step may, alternatively, involve a high energy media mill or an agitator bead mill, for example, the Netzch high energy media mill, or the DYNO-mill (Willy A. Bachofen AG, Switzerland). Alternatively the milling may be a dry coating high energy process such as a MechanoFusion system (Hosokawa Micron Ltd) or a Hybridizer (Nara).

Other possible milling devices include air jet mills, pin mills, hammer mills, knife mills, ultracentrifugal mills and pestle and mortar mills.

Especially preferred methods are those involving the MechanoFusion, Hybridiser and Cyclomix instruments.

Other suitable methods include ball and high energy media mills which are also capable of providing the desired high shear force and compressive stresses between surfaces, although as the clearance gap is not controlled, the coating process may be less well controlled than for MechanoFusion milling and some problems such as a degree of undesired re-agglomeration may occur. These media mills may be rotational, vibrational, agitational, centrifugal or planetary in nature.

It has been observed in some cases that when ball milling active particles with additive material, a fine powder is not produced. Instead the powder was compacted on the walls of the mill by the action of the mill. That has inhibited the milling action and prevented the preparation of the composite active particles. That problem occurred particularly when certain additive materials were used, in cases where the additive material was present in small proportions (typically < 2%), in cases where the milling balls were relatively small (typically < 3mm), in cases where the milling speed was too slow and where the starting particles were too fine. To prevent this occurring it is advantageous to ball mill in a liquid medium. The liquid medium reduces the tendency to compaction, assists the dispersal of additive material and improves any milling action.

The liquid medium may be high or low volatility and of any solid content as long as it does not dissolve the active particles to any significant degree and its viscosity is not so high that it prevents effective milling. The liquid medium preferably is not aqueous. The liquid is preferably one in which the additive material is substantially insoluble but some degree of solubility may be acceptable as long as there is sufficient additive material present that undissolved particles of additive material remain. Suitable liquid media include diethylether, acetone, cyclohexane, ethanol, isopropanol or dichloromethane. Liquid media are preferred which are non-flammable, for example dichloromethane and fluorinated hydrocarbons, especially fluorinated hydrocarbons which are suitable for use as propellants in inhalers.

Alternative Methods for Preparing Heparin Particles

Clearly there are other known techniques for forming fine particles comprising heparin and a FCA. Such techniques include, for example, techniques using supercritical fluids (SCFs), which have been explored for many years for particle production purposes. Similar to the spray-drying technique, this technique provides a direct formation of micron-sized particles suitable for inhalation powders. The most commonly used supercritical fluid technologies for particle production are rapid expansion of supercritical solutions (RESS) and supercritical antisolvent (SAS) or gas antisolvent (GAS) methods.

RESS is based on a rapid expansion of a SCF. The process involves dissolving the drug mixture in a SCF, followed by a rapid expansion of the fluid causing the compound to precipitate. This technique is capable of producing uniform particles, with control on the size distribution and morphology of particles. However, this technique is limited by the fact that most drugs have low solubility in the SCFs.

SAS is a recrystallisation process that relies on the capability of SCFs to act as an antisolvent to precipitate particles within a liquid solution. Unlike in the RESS technique, SAS does not require a high solubility of the drug compounds in the SCFs. Therefore, SAS is more commercially viable for powder production.

Recently a solution enhanced dispersion by supercritical fluids (SEDS) was introduced, see for example patent publications GB 2322326, WO 95/01324, WO 95/01221, US 5,851,453 and WO 96/00610. This technique is based on simultaneous dispersion, solvent extraction and particle formation in a highly turbulent flow. SEDS is capable of generating uncharged and crystalline product, with the capability of controlling particle size and size distribution by manipulating process conditions.

Another approach is the technique known as emulsion precipitation. This method can be used to prepare fine particles of heparin and one or more FCAs.

Delivery Devices and Doses

The dry powder compositions of the present invention are preferably delivered by an inhaler device, most preferably by a dry powder inhaler (DPI). This type of inhaler is commonly used for pulmonary administration of a dry powder formulation. Thus, according to a further aspect of the invention, a DPI is provided, for dispensing the heparin composition of the present invention.

The DPI may include a reservoir for holding the powder formulation and a metering mechanism for metering out individual doses of the formulation from the reservoir.

Alternatively, the dry powder inhaler may be arranged to use pre-metered doses of the formulation packaged, for example, in hard or soft gelatin capsules or blister packs. The Rotahaler (GlaxoSmithKline) and the Monohaler (Miat) are examples of this type of dry powder inhaler. The invention also provides a metered dose of the formulation contained, for example, in a hard or soft gelatin capsule or blister pack.

Preferably, the inhaler is arranged to dispense one or more doses of the formulation, each dose comprising an effective amount of heparin to be made available for inhalation. The dose may comprise not more than 100mg of heparin, preferably not more than 50mg, more preferably not more than 25mg and most preferably not more than 20mg of heparin. The dose may comprise at least 20mg of heparin, preferably at least 50mg. A preferred dose comprises 70-80mg heparin.

In another embodiment of the present invention, the DPI is adapted to deliver heparin to the deep lung of a patient at a dose of at least 5,000 IU.

According to another aspect of the present invention, a package is provided for use in a DPI containing as amount of the heparin composition which comprises at least 20mg of heparin. Preferably, the DPI according to the invention is arranged to use a package according to the invention.

According to a yet further aspect of the present invention, the compositions according to the invention are used for use in therapy. Preferably, they are for use in treating pulmonary diseases or DVT, as discussed above.

Claims

1. A pharmaceutical composition comprising heparin, wherein the composition is a dry powder for administration by pulmonary inhalation.

2. A pharmaceutical composition as claimed in claim 1, wherein the heparin comprises a high molecular weight fraction of heparin.

3. A pharmaceutical composition as claimed in either of the preceding claims, wherein the heparin comprises a heparin analogue or derivative, and preferably wherein the heparin comprises sulphated heparin.

4. A pharmaceutical composition as claimed in any one of the preceding claims, wherein the composition has a fine particle fraction (<5μm) of at least 50%, and preferably between 70 and 99% or between 80 and 99%.

5. A pharmaceutical composition as claimed in any one of the preceding claims, wherein the composition has a fine particle dose of between 50 and 90%, and preferably between 60 and 70%.

6. A pharmaceutical composition as claimed in any one of the preceding claims, comprising particles of heparin and a force control agent.

7. A pharmaceutical composition as claimed in claim 6, wherein the force control agent is an amino acid or peptide, or derivatives thereof, a phospholipid or a metal stearate.

8. A pharmaceutical composition as claimed in claim 7, wherein the force control agent is leucine, lysine, cysteine, or mixtures thereof.

9. A pharmaceutical composition as claimed in claim 6, wherein the force control agent is included in an amount of up to 50% w/w, preferably less than 10% w/w, and more preferably less than 5% w/w.

10. A pharmaceutical composition as claimed in any of the preceding claims, wherein the composition comprises heparin particles having a MMAD of less than 10μm.

11. A pharmaceutical composition as claimed in claim 10, wherein the heparin particles have a MMAD of 2-5μm or a MMAD of less than 2μm.

12. A pharmaceutical composition as claimed in any one of the preceding claims, wherein the composition further comprises carrier particles, preferably wherein the carrier particles have a particle size of at least 20μm.

13. A method of preparing a pharmaceutical composition as claimed in any one of the preceding claims, wherein heparin and a force control agent are made into fine composite particles, with at least some of the force control agent being present on the surface of the particles.

14. A method as claimed in claim 13, wherein the heparin and force control agent are co-spray dried.

15. A method as claimed in claim 14, wherein the solid content of heparin is no more than 5% w/w.

16. A method as claimed in any one of claims 14 and 15, wherein the heparin is co-spray dried with 1-50% w/w force control agent.

17. A method as claimed in claim 16, wherein the heparin is co-spray dried with less than 10% w/w force control agent, and preferably less than 5% w/w.

18. A method as claimed in any one of claims 14 to 17, wherein the heparin and force control agent are spray dried using a spray drier comprising a 2-fluid nozzle.

19. A method as claimed in any one of claims 14 to 17, wherein the heparin and force control agent are spray dried using a spray drier comprising a means for producing droplets moving at a controlled velocity and of a predetermined size.

20. A method as claimed in claim 19, wherein the spray drier comprises an ultrasonic nebuliser.

21. A method as claimed in any one of claims 13-20, wherein the method comprises adjusting the moisture content of the heparin and force control agent particles.

22. A method as claimed in claim 21, wherein adjusting the moisture content involves a secondary drying step.

23. A method as claimed in claim 22, wherein the secondary drying step involves drying the spray dried particles under a vacuum or freeze-drying the particles.

24. A method as claimed in claim 21, wherein moisture is added to the heparin and force control agent particles.

25. A pharmaceutical composition as claimed in any one of claims 1-12, for use in therapy.

26. A pharmaceutical composition as claimed in claim 25, for treating a pulmonary disease.

27. A pharmaceutical composition as claimed in claim 26, wherein the pulmonary disease involves hypersecretion of mucus or abnormal viscoelasticity of mucus.

28. A pharmaceutical composition as claimed in either of claims 26 or 27, wherein the pulmonary disease is chronic bronchitis, acute asthma, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) or bronchiectasis.

29. A pharmaceutical composition as claimed in claim 25, for treating deep vein thrombosis.

30. A method of treating a pulmonary disease comprising the administration of a therapeutically effective amount of a pharmaceutical composition as claimed in any one of claims 1-12 to a subject in need of such treatment.

31. A method of treating deep vein thrombosis comprising the administration of a therapeutically effective amount of a pharmaceutical composition as claimed in any one of claims 1-12 to a subject in need of such treatment.

Abstract

Pharmaceutical Compositions

The present invention relates to improvements in pharmaceutical compositions comprising the pharmaceutically active agent heparin, for administration by pulmonary inhalation. In particular, the invention relates to dry powder compositions comprising heparin for pulmonary inhalation.

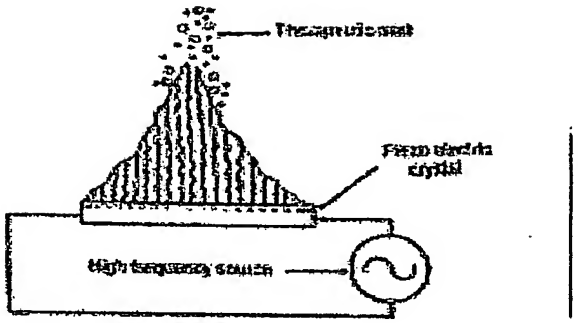


Figure 1

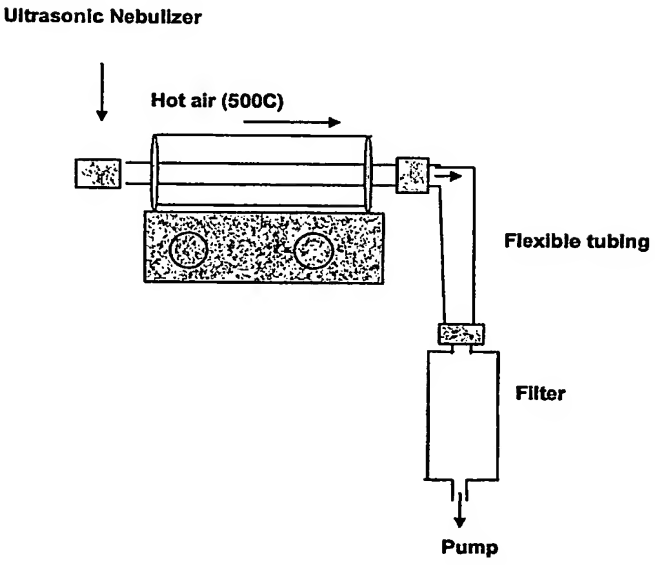
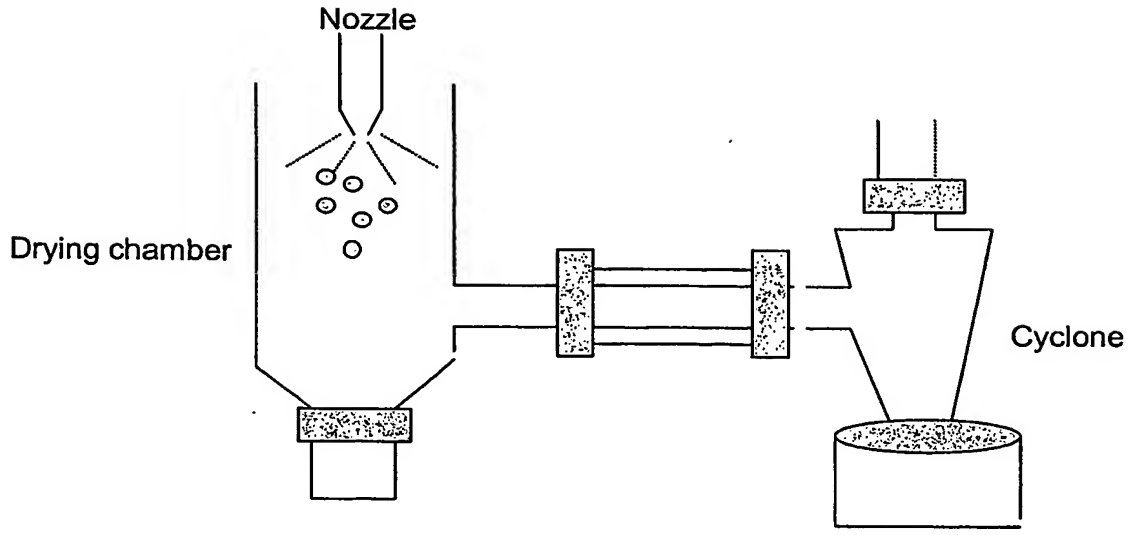


Figure 2



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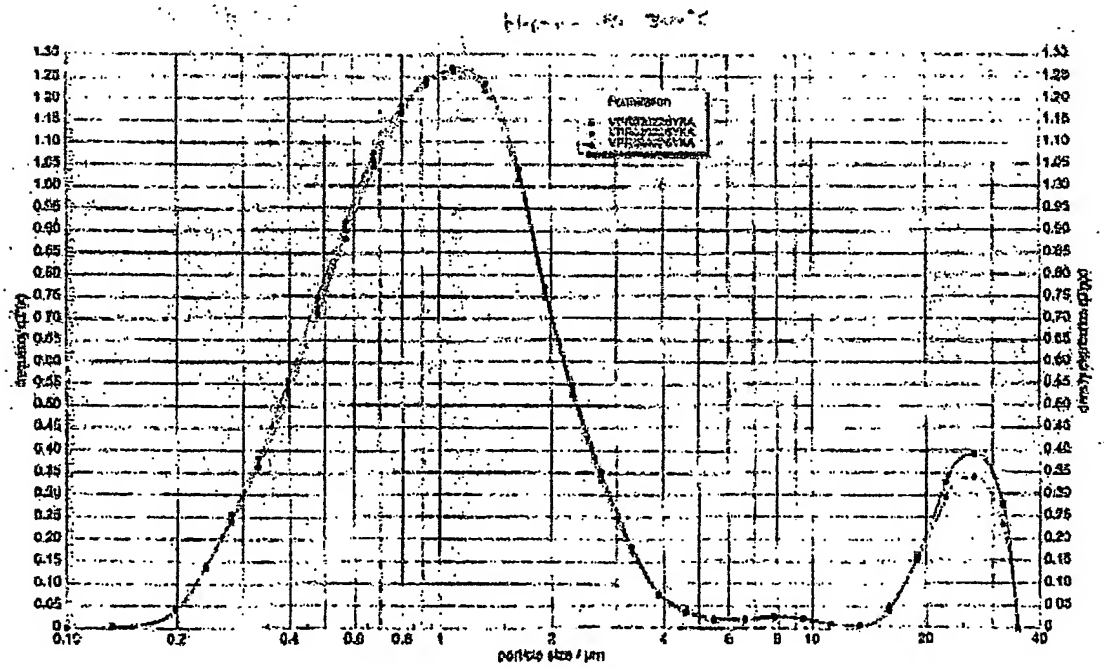

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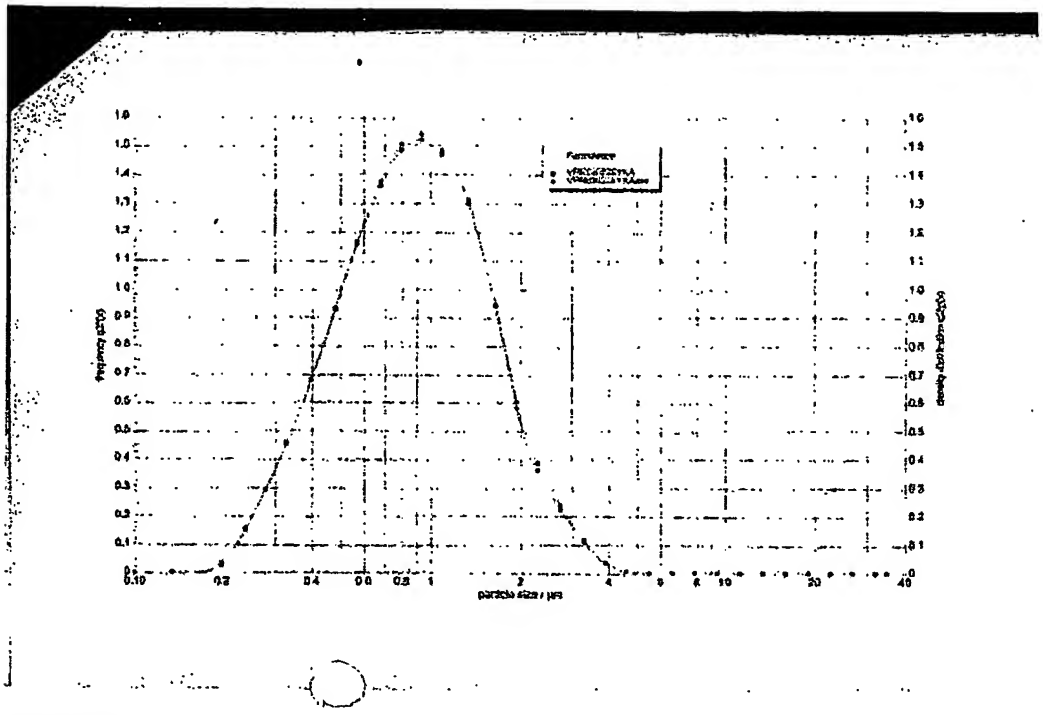

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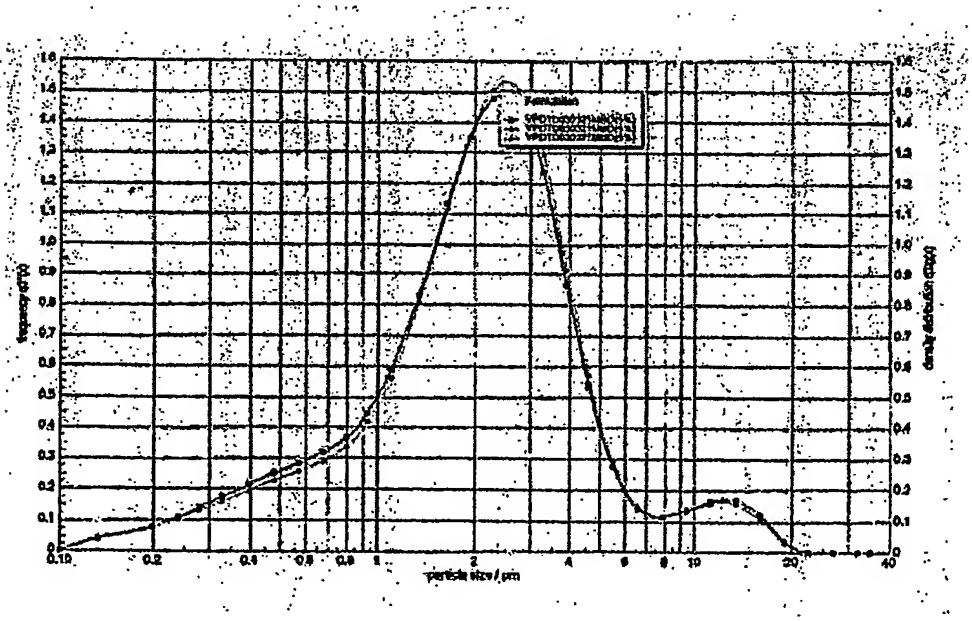

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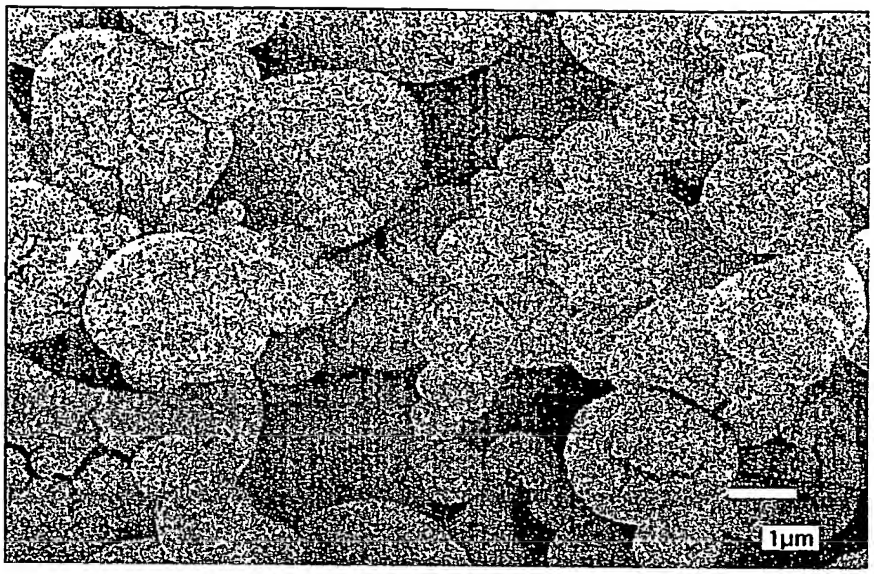

Figure 7a

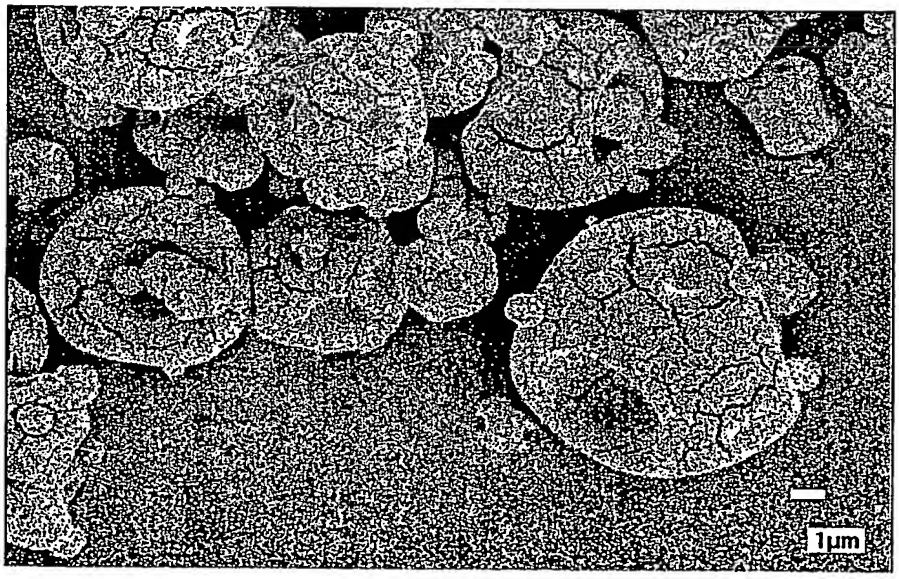

Figure 7b

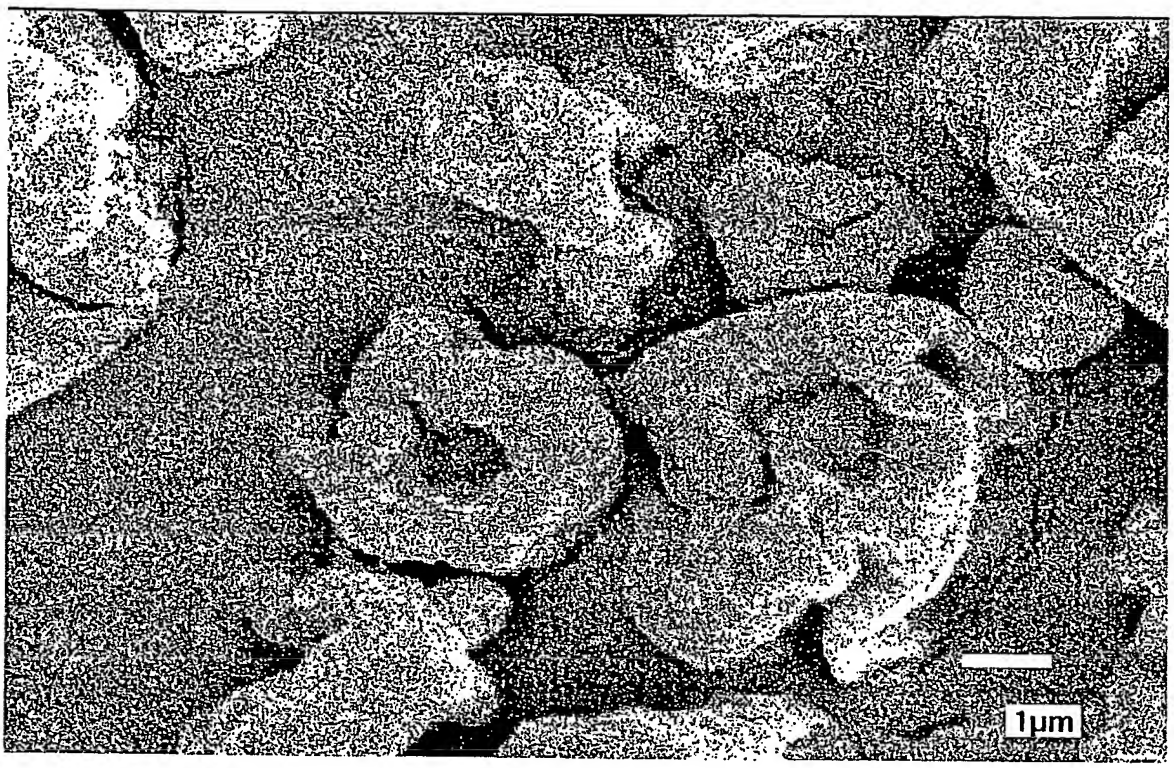

Figure 7c

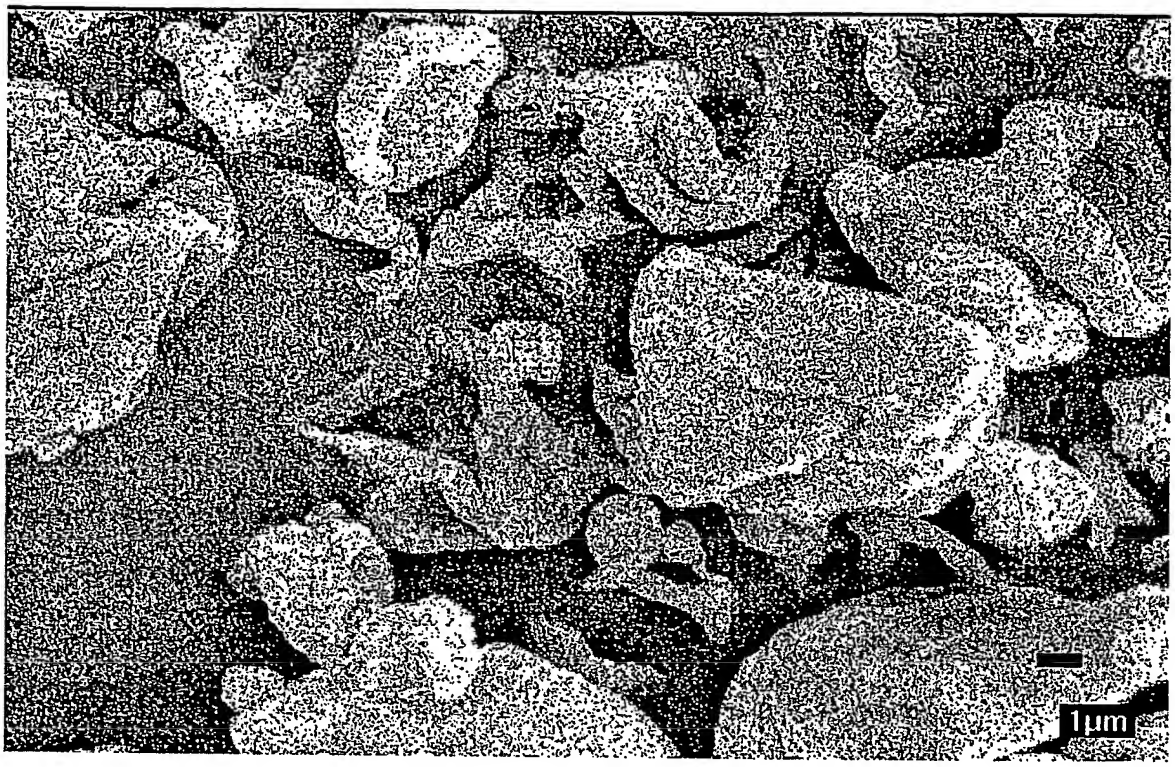

Figure 7d

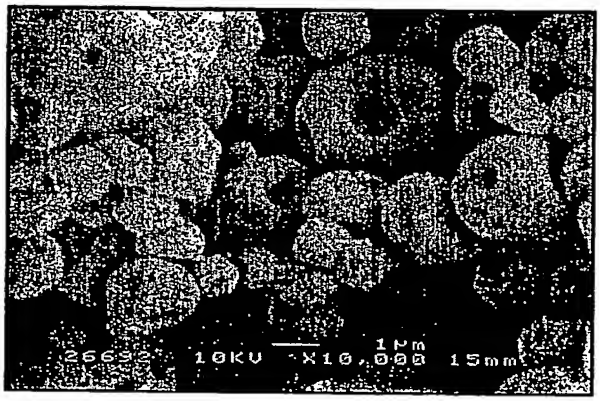

Figure 7e

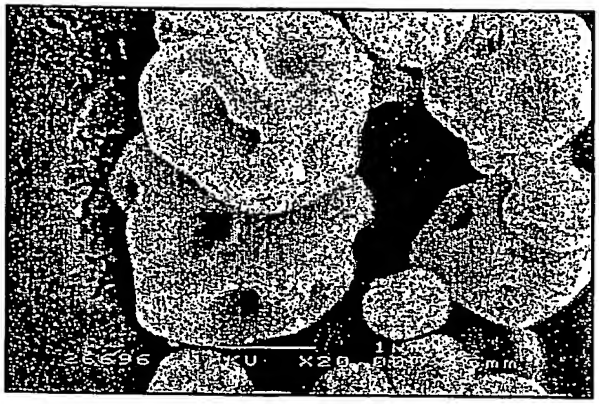

Figure 7f

Figure 7g

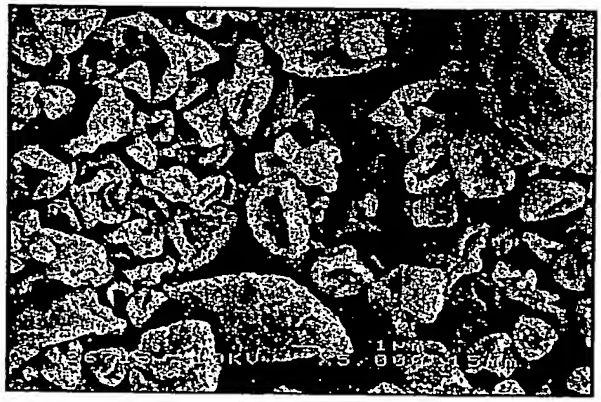

Figure 7h

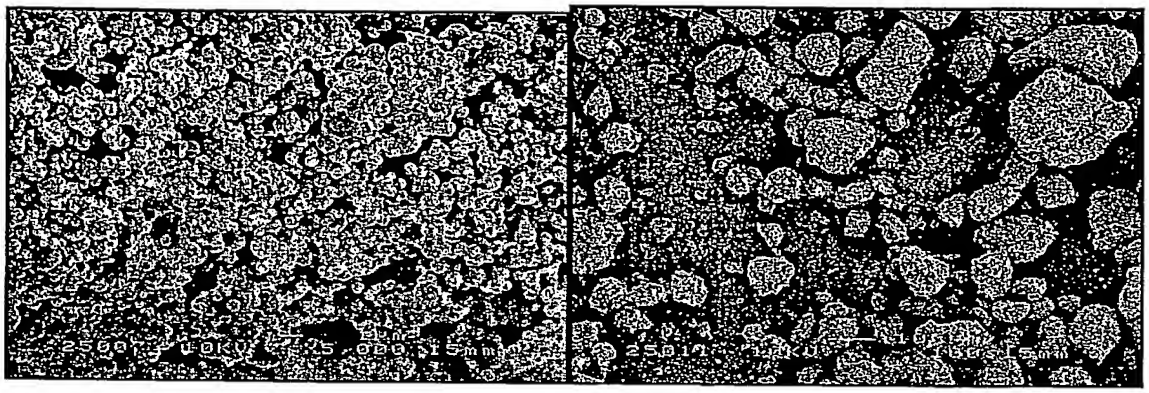

Figure 8a

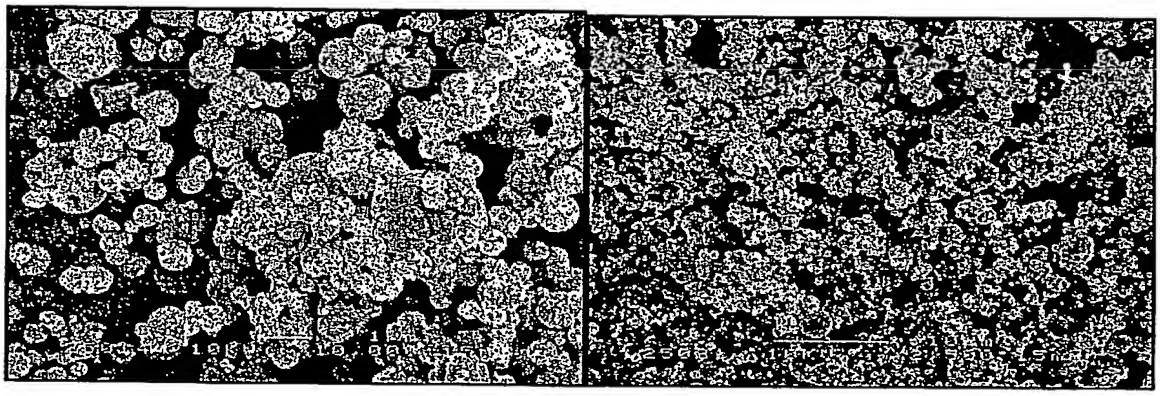

Figure 8b

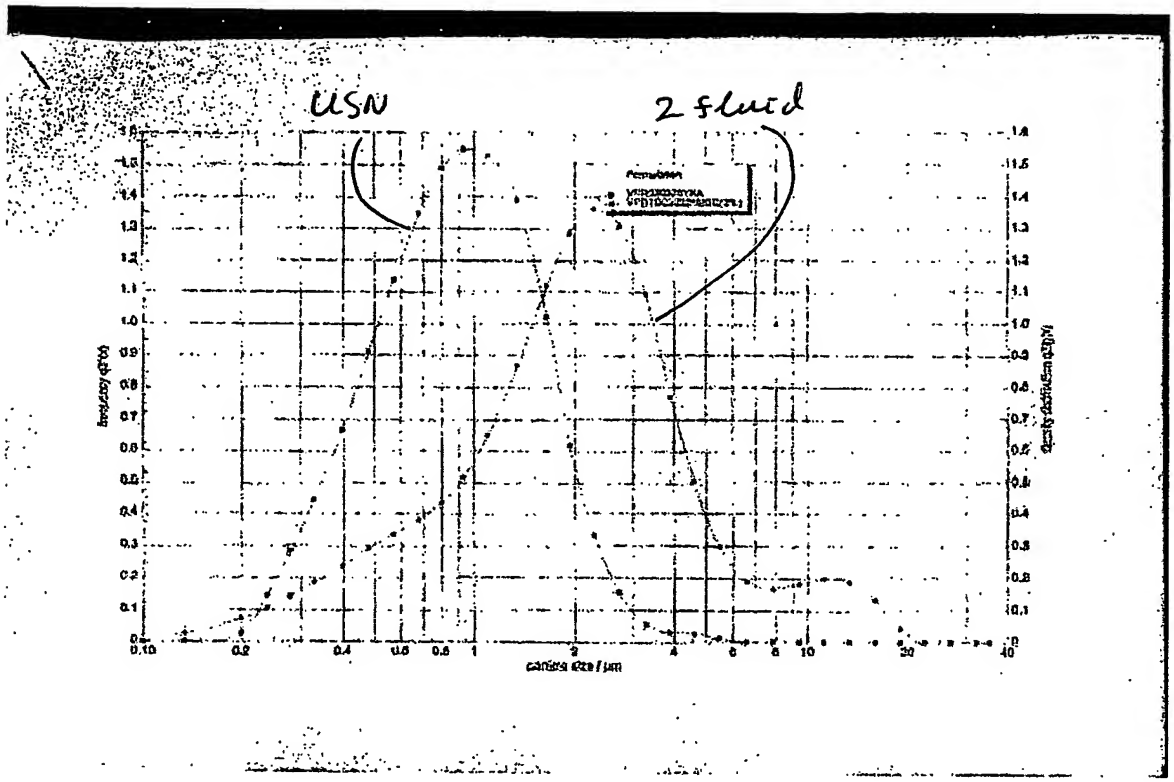

Figure 9a

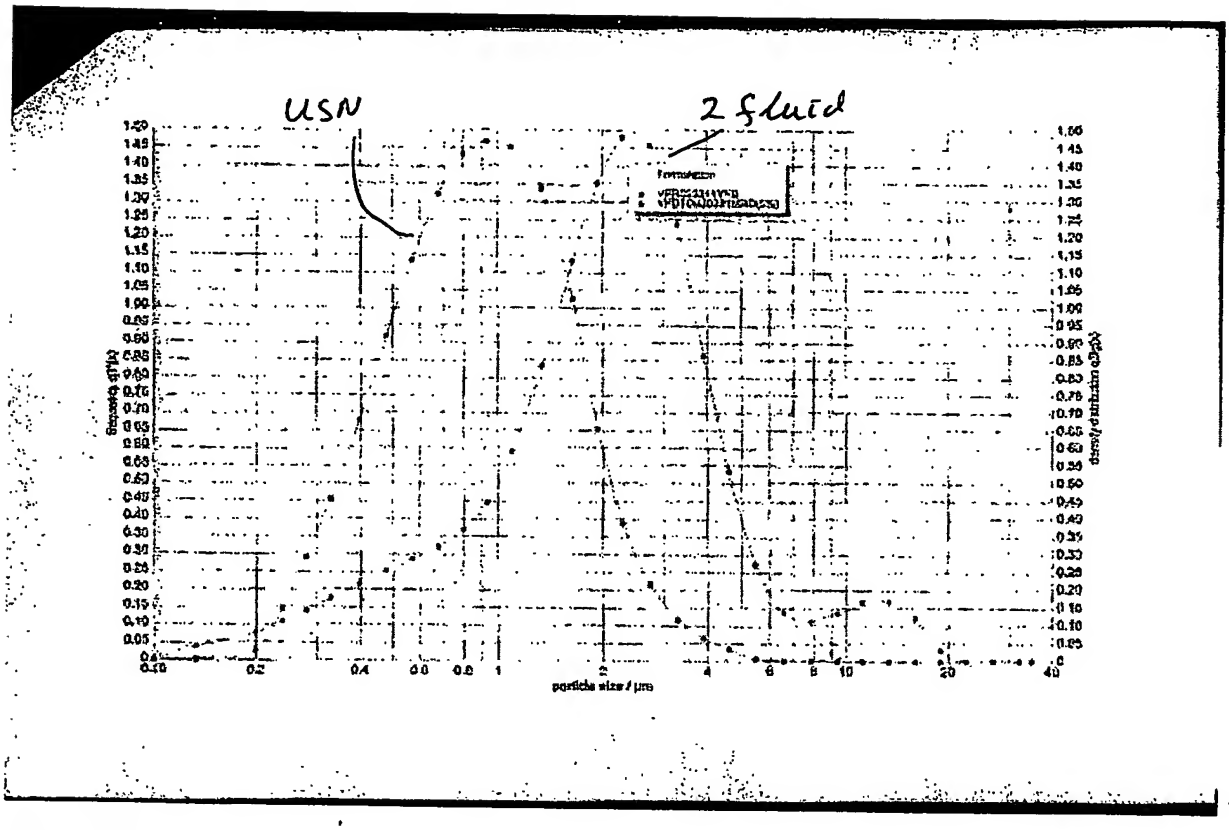

Figure 9b

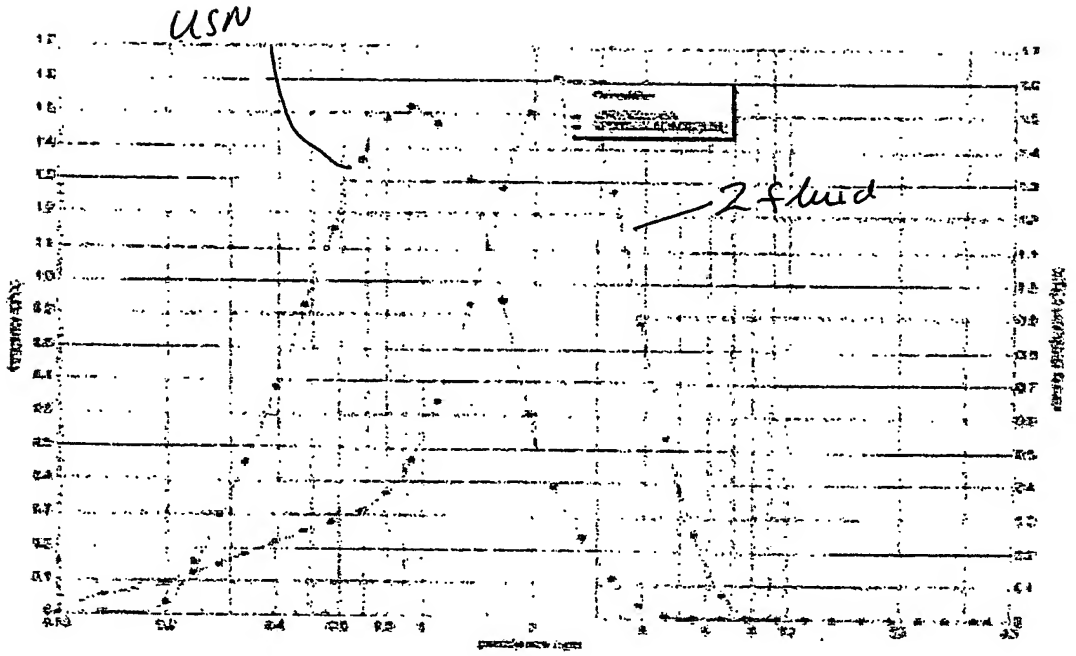

Figure 9c

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